VANCOUVER HOSPITAL & Health Sciences Centre

DRUG AND THERAPEUTICS NEWSLETTER

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In This Issue...

All formulary changes and policy/procedure updates have been approved by the Drugs and Therapeutics (D&T) Committee and Medical & Academic Advisory Council (MAAC).

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Changes to Formulary

Additions

- **Bupropion sustained release 100mg, 150mg tablets (Wellbutrin® SR)**
- antidepressant
- see page 3 for drug review

2. Piperacillin/tazobactam 2g/0.25g, 3g/0.375g, 4g/0.5g vials (Tazocin®)

- broad-spectrum, semi-synthetic penicillin antibiotic and a beta-lactamase inhibitor
- see page 5 for drug review

Deletions

2. Piperacillin 3g, 4g vials (Pipracil®)

- alternative: Piperacillin/tazobactam

Updated Policies/Procedures

2. Switch to Alteplase (r-tPA) for Occluded Central Venous Catheters

On January 31, 2000, alteplase (r-tPA) replaced streptokinase as the standard drug to treat occluded catheters. The reason for this change was concern for the potential for hypersensitivity reactions (including anaphylaxis) when repeat courses of this drug are administered. While there is limited literature regarding this complication from low dose streptokinase when used to lyse catheter clots, this complication has been reported when streptokinase is used systemically for other indications.

The effectiveness of alteplase to clear blocked central venous catheters has been demonstrated in clinical trials. Pharmaceutical Sciences CSU now prepares aliquots of alteplase in 2mg/2mL syringes. The syringes are stable for 6 months when frozen at -20º C and require ~20 minutes to thaw at room temperature. The volume of alteplase solution to be administered is equivalent to the internal volume of the occluded catheter + 0.2mL. The solution is instilled over 1 hour and may be repeated once, if necessary. The extra 0.2mL is added to ensure that alteplase reaches the

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tip of the catheter where a fibrin sheath may exist.

2. Quinapril and Lisinopril Interchange to Ramipril

Captopril, enalapril, and ramipril are angiotensin-converting enzyme inhibitors (ACEI) that are on formulary at VHHSC. Ramipril is a frequently prescribed drug in the community sector, although prescriptions for quinapril and lisinopril are also relatively common. As a result, a therapeutic interchange policy will be instituted on March 27, 2000, whereby all inpatient prescriptions for quinapril and lisinopril will be interchanged to a therapeutically equivalent dose of ramipril at the same dosing interval (Table 1). Should a physician wish to continue therapy with a non-formulary ACEI, the prescriber may override this policy by stating "no substitution".

3. Revised Drug Administration Policies

- The current list of restricted prescribers for **ursodiol** (Ursofalk®) has been expanded to include all members of the **Departments of Gastroenterology and Hematology**.

Table 1. Quinapril/Lisinopril Conversion to Ramipril

Drug	Equivalent Dose
Ramipril (Altace®)	2.5mg
Quinapril (Accupril®)	10mg
Lisinopril (Prinivil®, Zestril®)	10mg

- **Tinzaparin** may be prescribed for the **treatment of pulmonary embolism** as well as deep vein thrombosis.
- The use of **vasopressin** for the management of **vasodilatory septic shock** has been extended to include both **ICU-2 and CSICU**.
- For **dobutamine** infusions, the requirement that a **physician must be present** for the **first 15 minutes** of the infusion now applies to **non-critical care areas** only.
- **Cardiothoracic (CT) technologists** are approved to **start peripheral IV infusions** and **inject into and flush heparin locks**.
- **Amiodarone** infusions may be administered in critical care areas as well as **SICU**.
- **Pamidronate** approved concentration and rate has been increased to **90mg/250mL over 1 hr.**
- **Esmolol** has been approved for use as an **antidote for dobutamine during myocardial perfusion imaging** in nuclear medicine.

Pharmacy Awards

Several *members* of Pharmaceutical Sciences CSU were recipients of the Canadian Society of Hospital Pharmacists (CSHP) 1999 awards for excellence:

***3. Saira Alladina*.** (Roche/CSHP B.C. Interhospital Competition for Highest Ranked Resident).

***2. Emily Ho*.** (Pharmacia & Upjohn/CSHP Award for Highest Ranked B.C. Residency Project) "Development of a clinical pathway for the management of pediatric croup."

3. Subcutaneous loxapine: a new route of administration. *C Sauder,* P Porterfield, *Dr. KF Shalansky*, Dr. K Tong (Sabex/CSHP National Research Competition for Palliative Care).

4. Evaluation of the effect of intravenous l-carnitine on quality of life in chronic hemodialysis patients. *J Semeniuk*, *Dr. KF Shalansky*, N Taylor, Dr. J Jastrzebski, Dr. EC Cameron (Merck-Frosst/CSHP National Research Competition Award for Rational Drug Therapy).

5. Economic impact of standardized orders for antimicrobial prophylaxis (S.O.A.P.) program. *L Frighetto, Dr. C Marra, Dr. P Jewesson* (Roche/CSHP National Research Competition Award for Specialties in Pharmacy Practice).

6. A novel ciprofloxacin stepdown program in the treatment of high-risk febrile neutropenia: a clinical and economic analysis. *Dr. C Marra, L Frighetto*, C Quaia, *Dr. D Warkentin, Dr. F Marra*, Dr. M de Lemos, *Dr. P Jewesson* (Novartis/CSHP National Research Competition Award for Pharmacoeconomics).

Pharmacy Research Grants

1. 1999/00 VHHSC Interdisciplinary Research Grant ($10,000.00) for the project:
- **"Treatment of catheter-related bloodstream infection caused by coagulase negative staphylococcus in the critically ill: removal of catheter followed by 2 days compared with 7 days of vancomycin."** *Dr. J de Lemos, N Alikashani*, Dr. G Stiver, Dr. E Bryce, Dr. J Ronco

2. B.C. Health Research Foundation Grant ($30,000.00) for the project:
- **"Pharmacokinetics and pharmaco-dynamics of mycophenolate in the early period following lung, heart, and heart-lung transplants."** Dr. M Ensom, Dr. R Levy, Dr. A Ignaszewski, *Dr. N Partovi*

New Drug/Drug Products

Bupropion SR (Wellbutrin® SR)

Alan Low, Pharm.D., Michelle Guy, B.Sc. (Pharm)
reviewed by Dr. R. Raina, Department of Psychiatry

Bupropion sustained release (SR) has been recently added to the formulary at VHHSC for the treatment of depression. This drug belongs to the amino-ketone class and is not related to any of the currently marketed antidepressant agents, such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), or monoamine oxidase inhibitors (MAOIs).[1,2] Although used initially to treat depression, bupropion has also been studied and is approved for use as an aid in smoking cessation, by decreasing the cravings associated with nicotine withdrawal.[3.4] In Canada, bupropion SR is marketed under the name Wellbutrin® SR for depression and Zyban® for smoking cessation. Bupropion has also been studied, but is not yet approved, for the treatment of attention deficit hyperactivity disorder[5].

Clinical Benefits

While there are few direct comparative trials, bupropion is superior to placebo and appears to be similar in efficacy to SSRIs, TCAs[3,6], and specifically amitriptyline[7], doxepin[8], trazodone[9], sertraline[10,11] and fluoxetine[12].

Unlike other antidepressants, bupropion enhances dopamine and norepinephrine levels by inhibiting their reuptake and does not appear to act on the serotonin system.[1] It is thought that this lack of effect on the serotonin system results in fewer side effects compared to SSRIs, specifically sexual dysfunction and gastrointestinal disturbances.[3,10] Bupropion has been added to SSRI therapy to help alleviate sexual dysfunction caused by the latter.[13] As well, bupropion causes little or no anticholinergic side effects, and less cardiovascular effects (orthostasis) and weight gain compared to TCAs.[6]

Bupropion is primarily metabolized to active metabolites by the cytochrome 2B6 isoenzymes. It has minimal effect on the activity of cytochrome p450 isoenzymes and thus there is decreased chance of drug interactions that are common with the SSRI's.[1] There is suggestion that bupropion may inhibit the activity of the isoenzyme 2D6, leading to increased levels of some TCAs, but further study to confirm this interaction is required.

Bupropion's acquisition cost appears to be lower than that of other newer antidepressants (Table 2). However, direct cost comparisons must be made with caution as equivalent doses between these agents have yet to be established.

Clinical Risks

There have been reports of a higher frequency of seizure activity with bupropion compared to other antidepressants. However, these reports were based mainly on the immediate release formulation that was previously marketed in other countries. With the sustained release formulation, the seizure rate was found to be 0.1% at doses up to 300mg SR per day.[2,3,14] This rate is similar to that of the newer antidepressants e.g. SSRIs, venlafaxine, nefazodone and is lower than that reported for TCAs. To date, there have been no reports of serotonin syndrome associated with bupropion.[15]

Combined use of bupropion with other antidepressants has not been well studied. There are published reports of the successful addition of bupropion to existing SSRI therapy for thetreatment of SSRI-induced sexual dysfunction.[13,16] However, its use in combination with MAOIs is contraindicated based on animal studies showing toxicity.[15] The most commonly reported adverse effects of bupropion (Table 2) appear to be dose-related.[3,4,10]

Dosage

Dosing is initiated at 100mg of bupropion SR once daily and may be increased to 300mg/day (150mg

Table 2. Comparison of side effects and cost of selected antidepressants[14, 17-19]

Drug	Common Side Effects[a]	Usual Dose/Day	Cost/Day[b]
Atypicals			
Bupropion SR	**Nervousness, agitation, tremors, insomnia, dry mouth, nausea, constipation, sweating**	**100-300mg**	**$0.53-1.60**
Nefazodone	Dizziness, fatigue, confusion, vision disturbances, dry mouth, nausea, constipation, drowsiness	100-500mg	$0.80-4.00
Venlafaxine	Nausea, drowsiness, nervousness, dizziness, insomnia, anorexia, dry mouth, constipation, sweating	37.5-150mg	$0.78-3.12
TCAs			
Amitriptyline	Dizziness, drowsiness, headache, dry mouth, constipation, weight gain, sweating, orthostasis, blurred vision	75-150mg	$0.03-0.06
Nortriptyline	Dizziness, drowsiness, headache, dry mouth, constipation, weight gain, sweating, orthostasis	50-150mg	$0.36-1.08
SSRIs			
Sertraline	Tremors, nausea, diarrhea, insomnia, drowsiness, dizziness, sweating, sexual dysfunction	25-200mg	$0.80-3.10
Fluoxetine	Nausea, insomnia, nervousness, tremors, drowsiness, fatigue, anorexia, sexual dysfunction	20-80mg	$0.74-2.96
Fluvoxamine	Drowsiness, agitation, tremor, nausea, constipation, anorexia, sexual dysfunction	50-300mg	$0.76-4.56
Paroxetine	Nausea, drowsiness, tremors, dizziness, dry mouth, sweating, sexual dysfunction, insomnia	20-50mg	$1.59-4.77
MAOI			
Phenelzine[c]	edema, orthostasis, insomnia, sexual dysfunction, caution with foods containing tyramine	45-90mg	$0.90-1.80

[a] >5% placebo-adjusted incidence rate of adverse effects; [b] based on VHHSC acquisition costs; [c] non-formulary agent at VHHSC

SR bid), based on clinical response. Food has no clinically significant effect on bupropion's disposition. The dose of bupropion should be increased gradually, in divided doses, and should not exceed 450mg/day.[4]

Clinical Use

Owing to its side effect profile, bupropion appears to be useful in the treatment of depression in younger patients who do not have a component of anxiety, who have experienced sexual dysfunction with other agents and may benefit from bupropion treatment. Bupropion may also be considered in geriatric patients where the risks of TCA-related cardiotoxicity and anticholinergic side effects must be avoided. Further clinical trials are needed to determine its use in comparison with the other newer agents (e.g. SSRIs, atypicals) and combination therapy.

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Piperacillin/Tazobactam (Tazocin®)

Fawziah Marra, PharmD, Luciana Frighetto, B.Sc(Pharm), Carlo Marra, Pharm.D., Peter Jewesson, Ph.D.

Piperacillin, a semi-synthetic ureidopenicillin antibiotic, was introduced over a decade ago onto the North American market.[1] Although experience with this agent has been favourable, its spectrum of activity is relatively narrow and, therefore, application of this product has been limited. More recently, piperacillin has been combined with a beta-lactamase inhibitor, tazobactam, which extends the spectrum of activity of this drug.

Pharmacokinetic Properties

Following an intravenous injection, piperacillin/ tazobactam (P/T) is rapidly and widely distributed into body fluids and tissues while penetration into fatty tissues is limited. Therapeutic fluid and tissue concentrations are achieved in bone, skin, lung, gallbladder, colonic mucosa, pancreatic, gynecological and renal tissues, bile and peritoneal fluid.[2,3] Although there are no published studies evaluating the CSF penetration of P/T in humans, CSF concentration of piperacillin has been shown to be approximately 32% of serum concentration when administered as a continuous infusion to patients with bacterial meningitis.[4] Both piperacillin and P/T are not approved for use in meningitis; however, piperacillin has been employed for the treatment of pediatric meningitis caused by *Flavobacterium*.[5,6]

Piperacillin is metabolized to a minimally active metabolite while tazobactam has an inactive metabolite.[2,3] Renal excretion of unchanged piperacillin accounts for approximately 50-80% of the administered dose.[2] In patients with normal renal function, the serum elimination half-life of P/ T is 0.8 to 1 hour. Since renal clearance of P/T is decreased in patients with renal impairment, doses are adjusted according to creatinine clearance (Table 3).[2] The pharmacokinetics of P/ T are not markedly affected by patients in hepatic failure.

Antimicrobial Spectrum

The mechanism of action of P/T, like that of all beta-lactam antibiotics, involves the inhibition of bacterial peptidoglycan cell-wall synthesis.[7,8] Tazobactam, the beta-lactamase inhibitor, has good activity against staphylococcal penicillinase and many of the beta-lactamases isolated from gram-negative aerobic bacteria.[9-13]

Aerobic Gram-positive Pathogens: The addition of tazobactam increases piperacillin's activity against methicillin-susceptible strains of *Staphylococcus aureus (S.aureus),Streptococcus pneumoniae*, viridans streptococci, and group A, B, C, G streptococci, resulting in comparable activity to imipenem.[14-16] Similar to imipenem and piperacillin, P/T does not have activity against methicillin-resistant *S. aureus* (MRSA) and many strains of coagulase-negative staphylococci.[14-16] Tazobactam does not enhance piperacillin's activity against enterococci, thus the activity of the combination is the same as the parent drug.

Aerobic Gram-negative Pathogens: The addition of tazobactam extends the activity of piperacillin to include a large number of enterobacteriaceae including *Escherichia coli*, *Klebsiella* spp., *Haemophilus influenzae*, *Neisseria meningitidis, Neisseria gonorrhoea*, *Moraxella catarrhalis, Salmonella* spp., *Shigella* spp., *Proteus* spp., *Citrobacter* spp., *Acinetobacter* spp., *Serratia* spp. and *Enterobacter* spp.;[17] however, imipenem appears to demonstrate more activity against *Enterobacter* spp. than P/T.[15] Although P/T also exhibits good activity against *Pseudomonas aeruginosa,* the addition of tazobactam does not enhance the activity of piperacillin against *Pseudomonas* spp.. Combination therapy with an aminoglycoside or ciprofloxacin is recommended for infections involving this organism and for other serious gram-negative infections.[15,16] *Pseudomonas cepacia* and *Stenotrophomonas maltophilia* are intrinsically resistant to P/T (MIC > 32 mg/L).[16]

Anaerobes: P/T has excellent activity against the *B. fragilis* group including those that produce beta-lactamases, and other *Bacteriodes, Fusobacterium* species, *Peptostreptococcus* species and *Clostridium* species.[16,18,19] *Clostridium difficile* is usually only moderately susceptible or may even be resistant.[16] P/T is considered more active than cefoxitin and clindamycin and equivalent to imipenem against the *Bacteriodes* spp. and *Clostridium* spp..[15]

Comparison to Other Antibiotics

Several randomized, comparative clinical trials have been published that evaluate the efficacy of P/T for the treatment of intra-abdominal, pelvic inflammatory, lower respiratory tract, skin and soft tissue infections, and empiric treatment in febrile neutropenic patients.[20-34] Comparator regimens include imipenem, ticarcillin/ clavulanate, ampicillin combined with gentamicin and metronidazole, clindamycin and gentamicin, or ceftazidime and amikacin. P/T was reported to have at least equivalent efficacy to the alternative regimens with clinical cure rates of 41-98%.

In trials conducted in patients with hospital-acquired respiratory tract infections, clinical success was achieved in 51-87% of patients treated with P/T plus amikacin or P/T alone.[20-22] P/T plus amikacin was significantly more effective

than ceftazidime plus amikacin in patients with ventilator-associated pneumonia (51% vs 36% respectively).[22] P/T alone was as effective as imipenem in the treatment of patients with nosocomial pneumonia with clinical failure demonstrated in 17% and 29% of patients, respectively.[21] Clinical trials evaluating the efficacy of P/T for treatment of intra-abdominal infections showed that 12 grams daily of P/T had equivalent efficacy to gentamicin plus clindamycin, or gentamicin plus metronidazole and ampicillin.[23,24] Trials comparing the efficacy of P/T with imipenem for intra-abdominal infections have shown P/T 4g/0.5g IV Q8H to be as effective or better than imipenem 0.5g or 1g IV Q8H.[21,25-27] P/T (12-16g/day) in combination with an aminoglycoside has been compared to cetazidime or piperacilin plus an aminoglycoside for the treatment of febrile neutropenia.[28,29] Clinical success with P/T ranged from 41% to 61% compared to 54% to 60% for the comparator regimens. In skin/soft tissue[30], urinary tract[31,32] and gynecological[33] infections, P/T was as effective as the comparator regimens and achieved clinical success rates of above 85%.

To evaluate the formulary feasibility of substituting P/T for imipenem, a randomized, double-blind, single-centre study involving adult patients with serious bacterial infections was conducted at VGH in 1995/96.[34] One hundred and fifty treatment courses (75 P/T 4g/0.5g IV q6h vs. 75 imipenem 500mg IV Q6H, " concurrent antibiotics) were assessed. In the majority of cases, treatment discontinuation occurred as a result of a favourable treatment course outcome, stepdown to a narrower spectrum parenteral agent or stepdown to an oral agent and did not differ between study drugs (p=0.73). Clinical outcomes were deemed successful or improved for 68% of imipenem and 70% of the P/T treatment courses (p=0.54). Fifty-three percent of treatment courses were microbiologically confirmed. Of the 58 courses that were assessed for microbiological outcome, successful eradication of the causative pathogens did not differ between study drugs (96% imipenem; 90% P/T p=0.61). The proportion of treatment courses with at least one adverse event was also similar between the study drugs (p=1.0). Nausea and/or vomiting were observed more commonly in the imipenem arm (p=0.03). Discontinuation of therapy due to drug toxicity occurred in 16% of imipenem and 5% of P/T treatment courses (p=0.06). A subsequent pharmacoeconomic assessment of the trial data revealed that imipenem was a cost-effective alternative to P/T at the dosage regimens studied.[35] However, this finding was sensitive to plausible changes in both clinical and economic parameters.

In summary, P/T appears to represent a suitable alternative to imipenem for several clinical indications including intra-abdominal infections, pneumonia, febrile neutropenia, pelvic inflammatory disease and skin/soft tissue infections in which the causative pathogens are susceptible. P/T may also play a role in reducing bacterial resistance (e.g. vancomycin-resistant enterococci, MRSA) by displacing, and thus reducing cephalosporin use. The high use of cephalosporins in the hospital setting has been implicated as a major contributor to the development of antibiotic resistance.[36,37]

Adverse Effects

Pooled data from numerous clinical trials indicate that P/T is generally well tolerated and possesses a side effect profile similar to piperacillin alone.[38,39] Gastrointestinal disturbances including nausea, vomiting and diarrhea are relatively common, and headache and insomnia have been reported in up to 10% of patients.[39] Clinically significant increases in hepatic enzymes have been reported and increases in serum creatinine have been noted in up to 4.2% of patients on P/T compared to 0.5% of patients on imipenem.[38-40] Nephrotoxicity was not reported in any of the direct comparative clinical trials. Hypersensitivity reactions including rash, fever, urticaria and pruritus occur in less than 5% of patients. Infrequent hematological abnormalities include leukopenia, eosinophilia, anemia, thrombocytopenia and prolonged prothrombin time.[39]

Dosage and Cost

Recommended dosages for P/T for moderate to severe infections range from 4g/0.5 g every 6 to 8 hours. Table 3 compares the dose and acquisition costs of this drug as compared to imipenem. Current acquisition costs for other comparators include ceftazidime 2g IV q8H ($47.00/day) and ceftriaxone 2g IV Q24H ($67.00/day).

Recommended Indications and Formulary Status

Based upon a recommendation from the Antibiotic Use Subcommittee and the D&T Committee, P/T has been added to the formulary as a reserved

antimicrobial drug to replace piperacillin. P/T should be considered as an alternative to piperacillin or imipenem for the empiric or directed therapy of serious polymicrobial infections involving known or suspected susceptible pathogens. P/T can also be considered an alternative to cephalosporins (e.g. ceftazidime, ceftriaxone) for susceptible pathogens. P/T is not approved for surgical prophylaxis.

A Select Antimicrobial Information Notice (SAIN) will be sent with each treatment course and a clinical pharmacist will also monitor each treatment course. This agent provides another broad-spectrum alternative for the treatment of serious polymicrobial infections.

Table 3. Comparison of P/T amd Imipenem

Creatinine Clearance	Dose (Cost/day[a])	
(mL/min)	P/T	Imipenem
> 50	4g/0.5g IV q6-8h ($84.80-63.60)	500mg IV q6h ($97.52)
30-50	3g/0.375g IV q6-8h ($63.60-47.70)	500mg IV q8h ($73.14)
< 30	2g/0.25g IV q6-8h ($42.40-31.80)	500mg IV q12h ($48.76)
Hemodialysis	2g/0.25g IV q8h ($31.80)	500mg IV q12h ($48.76)

[a] based on VHHSC acquisitions costs

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Further references available upon request.

Adverse Drug Reaction Report 1999

There were a total of 41 suspected adverse drug reactions (ADRs) reported at VHHSC in 1999 (Table 4). Of note, 14 reactions were considered to have been the cause of hospitalization and 1 ADR resulted in death. The continued reporting of all suspected ADRs by nurses, physicians and pharmacists aids in an improved assessment of the magnitude and nature of adverse events. To notify Pharmacy of an ADR, either fill out a yellow ADR alert card, available on all nursing units, and send to Pharmaceutical Sciences CSU, or call local 62481 (VGH site) or local 27249 (UBC site). Pharmacists complete all ADR report forms and forward copies to the B.C. Regional ADR Centre. This Centre does preliminary analysis of the data and then forwards all reports to the Canadian ADR program in Ottawa who then forward them to the World Health Organization.

Table 4. Adverse Drug Reactions Reported in 1999

Drug	Suspected ADR	Drug	Suspected ADR
Allopurinol	erythema multiforme (1); generalized pruritic papular rash with fever, sore throat, sore mouth and lips (1)[a]	Imipenem	two seizures three hours apart (1)[a]
4-Aminopyridine	muscle spasms in legs (1); heart palpitations, elevated BP and liver enzymes (1)	Kai Ki Wan (herbal Prostate Gland Pills)	generalized pruritic, erythematous, maculopapular eruptions (1)
Amiodarone	elevated liver enzymes, thrombocytopenia and neutropenia (1)[a]	Ketorolac	GI bleed (1)[a]
Amoxicillin	swelling of lips/throat, SOB, urticaria (1)	Mefloquine	grand mal seizure (1)[a]
ASA plus Metronidazole	itchy rash over body and legs (1)	Methimazole	generalized urticarial, maculopapular rash (1)
Bupropion SR (Zyban®)	SOB, rash (2); lip/tongue swelling , maculopapular , pruritic rash (1)	Olanzapine	worsening of Parkinson's disease (1)[a]
Carbamazepine	neutropenia (1)[a]	Perphenazine	chills, shakes, sweats, "felt like jumping out of skin" (1)
Celecoxib Celecoxib plus Moclobemide	diffuse maculopapular rash (1); upper GI bleed (1)[a]; confusion, decreased mental acuity and mood (1)	Phenytoin Phenytoin plus Rifampin	symmetrical erythema with papules on upper torso sparing face and neck (1); thrombocytopenia (1)
Diclofenac (Novo brand contains cornstarch)	difficulty breathing (1), tolerated Apo brand	Prednisone/ Methylprednisolone	psychosis and psychomotor hyperactivity (1)
Digoxin plus Propafenone	visual hallucinations, inappropriate behaviour (1)	Propylthiouracil	generalized urticarial maculopapular rash (1)
Donepezil	worsening of Parkinson's disease and sialorrhea (1)	Sertraline	rash (diffuse plaques), pruritis (1)
Edrophonium	non-cardiogenic pulmonary edema (1)[a]	Sildenafil	chest pain (1)
Estrogen (CES) plus Medroxyprogesterone	deep vein thrombosis (1)[a]	Simvastatin plus Cyclosporine	acute myopathy and rhabdomyolysis (1)[a]
Gabapentin	swelling of shoulder with intermittent aching pain (1)	Sotalol	symptomatic bradycardia and hypotension (1)[a]
Gingko	cerebral hemorrhage (1)[a]	Testosterone undecanoate	ventricular fibrillation arrest (1)[a,b]
Ibuprofen	edema of tongue (1); lip and tongue swelling, pruritis (1)	Venlafaxine	impotence (1); postural hypotension (1)

[a]hospitalized due to ADR ; [b] death due to ADR