



THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

NEW DRUGS VII

Mirtazapine (Remeron®)

Approved indication: “Symptomatic relief of depressive illness.”¹

Mechanism of action: As with all antidepressants the mechanism of therapeutic benefit is unknown. It is an inhibitor of a number of receptors including adrenergic, serotonergic, histaminic and muscarinic. It is classified as an atypical antidepressant and is unrelated to tricyclics, selective serotonin reuptake inhibitors or monoamine oxidase inhibitors.

Pharmacokinetics: Mirtazapine is inactivated by liver metabolism. Mean half-life is 26 hrs for men and 37 hours for women; half-life is prolonged in the elderly and in the presence of liver and renal disease.¹

Evidence of efficacy: The effectiveness of mirtazapine for use longer than 6 weeks has not been systematically evaluated in controlled clinical trials. The one longer-term study only followed a subset of treatment responders, invalidating randomization and thus interpretation.² Two randomized controlled trials (RCT) claim an advantage for mirtazapine^{3,4} and one does not.⁵ Twelve randomized controlled trials⁵⁻¹⁸ and three meta-analyses¹⁹⁻²¹ evaluated mirtazapine compared to other antidepressants, including amitriptyline, clomipramine, doxepin, trazodone, paroxetine, citalopram and fluoxetine. The main efficacy measure was symptomatic improvement as indicated by a $\geq 50\%$ reduction from baseline in the Hamilton Depression Rating Scale (HAM-D) or by a score of ≤ 7 , signifying remission of depression. Between 20-40% of patients in these 5-6 week trials were lost to follow-up, weakening the validity of study results, and no consistent advantage or disadvantage was observed for mirtazapine. Doses of mirtazapine and comparators varied considerably between trials.

Adverse effects: The common and serious adverse effects (from the product monograph) expressed as absolute risk increase over placebo are as follows: **somnolence 36%, increased appetite 15%, dry mouth 10%, weight gain 10%, elevated cholesterol 8%**, constipation 6%, dizziness 4%, liver enzyme elevations (ALT >3 times normal) 2%, neutropenia 1.5%, mania/hypomania 0.2%, agranulocytosis 0.07%, and seizure 0.03%.¹



Dose and cost: Approved dose is 15-45 mg/day (\$0.69 - \$2.06/day).

The three least expensive antidepressants in B.C. are: amitriptyline (Elavil®, generic) 75-300 mg/day (\$0.04 - \$0.16/day), imipramine (Tofranil®, generic) 75-300 mg/day (\$0.05 - \$0.17/day) and trimipramine (Surmontil®, generic) 75-300 mg/day (\$0.55 - \$1.11/day).

The three most expensive antidepressants in B.C. are: sertraline (Zoloft®) 50-200 mg/day (\$1.31 - \$2.80/day), venlafaxine (Effexor®) 75-300 mg/day (\$1.64 - \$3.50/day) and paroxetine (Paxil®) 20-50 mg/day (\$1.76 - \$3.64/day).

CONCLUSION: Mirtazapine has no proven efficacy or safety advantage over other antidepressant therapies. **It has a prominent sedative effect and patients should be warned that it may cause mental or motor impairment.** Longer-term trials with adequate follow-up are needed.

Salmon-Calcitonin Nasal Spray (Miacalcin®)

Approved Indication: “Treatment of diagnosed postmenopausal osteoporosis in females greater than 5 years postmenopause with low bone mass relative to healthy premenopausal females.”²²

Mechanism of Action: Salmon-calcitonin inhibits bone resorption by reducing the activity of osteoclasts; it has 40-50 times more affinity for cell surface receptor binding sites than mammalian calcitonins. The mechanism of the acute analgesic effect of salmon-calcitonin is unknown.²³



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Pharmacokinetics: The bioavailability of salmon-calcitonin nasal spray is 3-50% relative to intramuscular administration. The drug is rapidly absorbed by the nasal mucosa. The elimination half-life is about 45 minutes.²²

Evidence of Efficacy: Two RCTs have assessed the efficacy of salmon calcitonin nasal spray on the rates of vertebral collapse (radiographically-detected) and non-vertebral fractures in postmenopausal women with bone mineral density (BMD) levels 2 standard deviations or more below mean values of 30 year old women.^{24, 25} The first RCT, a 2-year dose-response study, had a sample size too small to detect differences in fracture rates.

The PROOF study was a 5-year study that randomized participants with at least one vertebral collapse at baseline to receive 100, 200 or 400 IU of salmon-calcitonin, or placebo. The primary endpoint was the incidence of new vertebral collapse compared to placebo. In 817 patients with vertebral fractures at baseline and follow-up radiographs, 21.3% taking 200 or 400 IU salmon calcitonin vs. 29.6% taking placebo experienced ≥ 1 new collapse (RR 0.72 [0.54-0.96], ARR 8.3%, NNT = 12 for 3 years). **There was no effect of the drug on non-vertebral or symptomatic fractures.** Fifty-nine percent of the 1255 participants withdrew from the study prematurely.

Adverse Effects: Rhinitis (nasal congestion, nasal discharge, or sneezing) occurred in 22% of participants receiving salmon-calcitonin vs. 15% of placebo participants in the PROOF study (ARI 7%).

Dose and cost: The recommended dose is 200 IU (one spray) daily (\$1.48/day). Nostrils are to be alternated. It should be taken in conjunction with at least 1000 mg elemental calcium per day and 400 IU vitamin D per day.

Other drugs for the same indication are: etidronate (Didrocal[®]) one tablet daily (\$0.43/day), alendronate (Fosamax[®]) 10 mg daily (\$1.84/day), risedronate (Actonel[®]) 5 mg daily (\$1.93/day), raloxifene (Evista[®]) 60 mg daily (\$1.69/day).

CONCLUSION: Salmon-calcitonin nasal spray reduces radiographically-detected new vertebral collapse in patients with at least one vertebral collapse and low BMD (ARR 8.3%), but has no effect on non-vertebral fractures. **Long term compliance is poor, even in a trial setting.**

This Letter contains an assessment and synthesis of publications up to March 2002. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 50 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

Gatifloxacin (Tequin[®]) and Moxifloxacin (Avelox[®])

Approved Indications for both: "acute sinusitis, community-acquired pneumonia (CAP) and acute exacerbation of chronic bronchitis (AECB).^{26,27} Additional indications for gatifloxacin are uncomplicated and complicated UTI, pyelonephritis and uncomplicated gonorrhoea."²⁶

Mechanism of action: similar to other fluoroquinolone antibiotics.

Pharmacokinetics: Both are well absorbed with half-lives of 12 hours. Gatifloxacin is eliminated by the kidney and moxifloxacin is metabolized by the liver.^{26, 27}

Evidence of effectiveness: Gatifloxacin has been compared with other antibiotics in 9 double blind RCTs. Eight of these trials show clinical efficacy ranging from 88 to 98%, which was not different from levofloxacin, ofloxacin, clarithromycin and erythromycin in the treatment of acute sinusitis, CAP, AECB, UTI and gonorrhoea.²⁸⁻³⁵ In one trial, gatifloxacin was significantly more effective than cefuroxime axetil (ARR 12%) in the treatment of AECB.³⁶ Moxifloxacin has been compared with other antibiotics in 10 double blind RCTs. These trials show clinical efficacy for the treatment of acute sinusitis, CAP and AECB ranging from 88 to 97%, which was similar to levofloxacin, cefuroxime axetil, clarithromycin, amoxicillin, or azithromycin (87 to 95%).³⁷⁻⁴⁸

Adverse effects: Gatifloxacin and moxifloxacin have tolerability profiles similar to other fluoroquinolones. Adverse effects include: gastrointestinal upset [nausea, diarrhoea, vomiting and abdominal pain], headache, and dizziness. Adverse effects reported since marketing are ventricular tachycardia, renal failure, peripheral neuropathy, myositis, and tendonitis.^{26, 27}

Dose and cost: Gatifloxacin (Tequin[®]), 400mg once daily (\$5.36/day), Moxifloxacin (Avelox[®]), 400mg once daily (\$5.36/day), ciprofloxacin (Cipro[®]) 250 to 500 mg BID (\$4.76 – 5.40/day) ofloxacin* (Floxin[®], generic) 400 mg BID (\$3.81/day) levofloxacin* (Levaquin[®]), 250 to 500 mg daily (\$4.85 – 5.52/day). *See Therapeutics Letter #26

CONCLUSION: Gatifloxacin and moxifloxacin have no proven clinical advantages over other fluoroquinolones, macrolides or amoxicillin. **Based on cost they are not first choice drugs for their approved indications.**

RR – relative risk

ARR – absolute risk reduction

NNT – number needed to treat to prevent one event

ARI – absolute risk increase

References:

The references for this Therapeutics Letter are available along with the web version of this Letter on the TI web site: www.ti.ubc.ca.