



THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

NEW DRUGS VI

Rosiglitazone (Avandia[®])

Approved indication: To lower blood glucose in patients with type 2 diabetes not controlled by diet and exercise alone: 1) as monotherapy or 2) in addition to maximum doses of metformin.

Mechanism of action: Agonist for the peroxisome proliferator-activated receptor by which it decreases insulin resistance in muscle and adipose tissue and inhibits hepatic gluconeogenesis.

Pharmacokinetics: Well absorbed. Extensively metabolized in the liver. Half-life is 3-4 hours.

Evidence of effects on surrogate markers: Two 8-week RCTs have compared rosiglitazone to placebo^{1,2}. Pooled results comparing rosiglitazone (8 mg) to placebo show a 2.9 mmol/L decrease in fasting glucose, no significant effect on plasma insulin, a 14.7% increase in LDL cholesterol, no significant effect on HDL cholesterol, a 0.9 kg increase in weight and a 2.4% decrease in hematocrit. One 26 week RCT compared rosiglitazone to placebo in 348 patients with inadequate glucose control while receiving 2.5 g of metformin daily³. Rosiglitazone (8 mg) as compared to placebo decreased HbA1C by 1.2%, decreased fasting glucose by 2.9 mmol/L, had no effect on plasma insulin, increased LDL cholesterol by 14.8%, increased HDL cholesterol by 9%, increased weight by 3.1 kg, and decreased hematocrit by 2.5%.

Major adverse effects: In the trials edema occurred more commonly with rosiglitazone as compared to placebo (ARI=2.5%, NNH=40 for 0.5 yr). There was no significant hepatotoxicity reported in the published RCTs. The US FDA review states that 11 patients in pre-marketing trials had ALT levels greater than 3 times the upper limit of normal. Two case reports of severe hepatotoxicity in patients taking rosiglitazone have been published^{4,5}. The first drug in this class, troglitazone, was withdrawn from the US market after reports of 90 cases of liver failure, including 63 deaths, in the USA.

Dose and cost: Rosiglitazone 4-8 mg daily (either once daily or BID). Daily cost: \$2.46 - \$2.76.

Conclusion: In patients with type 2 diabetes rosiglitazone improves some surrogate markers and worsens others. Long-term trials are required to know whether this class of drugs reduces morbidity and mortality outcomes.



Tolterodine (Detrol[®])

Approved indication: Relief of symptoms in patients with overactive bladder, defined as increased urinary frequency (> 7/day) plus urgency and/or urge incontinence.

Mechanism of action: Competitive muscarinic receptor antagonist.

Pharmacokinetics: Well absorbed and extensively metabolized in the liver by CYP 2D6 to an active metabolite. Average half-life for tolterodine is 2.3 h and for active metabolite 3.3 h.

Evidence of efficacy: Two double-blind RCTs are available comparing the effectiveness of tolterodine, 2 mg BID, with oxybutynin (Ditropan[®]), 5 mg TID, and placebo^{6,7}. As compared to placebo, tolterodine and oxybutynin decreased frequency of micturition by 1.0 and 0.8 per day, respectively, and episodes of urge incontinence by 0.6 and 0.8 per day, respectively. **There was no significant difference in the proportion of patients who perceived an improvement in bladder symptoms: placebo 47%, tolterodine 50%, and oxybutynin 49%⁷.**

Major adverse effects: Dry mouth was the most common adverse effect: placebo 18%, tolterodine 40%, and oxybutynin 78%. Withdrawal due to adverse effects (primarily dry mouth) were greater with oxybutynin 19%, than tolterodine 7%, and placebo 8%.

Dose and cost: Tolterodine 1-2 mg BID, \$1.75 daily, oxybutynin 5 mg BID to TID \$0.54-\$0.81.

Conclusion: Tolterodine and oxybutynin have similar but limited efficacy in patients with overactive bladder symptoms. Dry mouth is a common side effect and occurs more frequently with oxybutynin (78%) than with tolterodine (40%).



Bupropion

(Wellbutrin SR[®], Zyban[®])

Approved indication: 1) Symptomatic relief of depressive illness (effectiveness for use > 8 weeks has not been evaluated in controlled trials). 2) As an aid to smoking cessation (6-7 weeks).

Mechanism of action: Bupropion is chemically related to sympathomimetic drugs and unrelated to other antidepressants. It blocks reuptake of noradrenaline and dopamine, but the mechanism for its clinical effects is unknown.

Pharmacokinetics: It is extensively metabolized by the liver to at least 3 active metabolites. Half-life of parent drug and active metabolites is 20 to 37 hrs.

Evidence of efficacy: Bupropion was introduced in the USA in 1985 and was withdrawn in 1986 because of an unacceptable incidence of seizures. In 1989 it was reintroduced in the USA (maximum dose of 450 mg daily). Bupropion was first approved in Canada in 1998 as an SR twice-daily formulation. In one RCT bupropion SR, 150 mg daily and 150 mg BID, were similar and more effective than placebo based on physician rated scores of depression at 8 weeks⁸. In 2 RCTs bupropion (150-400 mg/day) was similar in effectiveness to sertraline (50-200 mg/day) at 8 weeks, but the incidence of satisfaction with sexual functioning was less with sertraline (63%) than bupropion (79%) and placebo (78%)^{9,10}.

In an RCT of 615 smokers, bupropion, whether taken as 150 mg daily or 150 mg BID, was associated with the same 1 year lower point-prevalence abstinence rate (no smoking in the previous 7 days) of 23% as compared to placebo 12.4%, ARR=10.6%, NNT=9¹¹.

Major adverse effects: Withdrawals due to adverse events in the 4 trials occurred in 7.1% of patients on bupropion as compared to 2.7% of patients on placebo, ARI= 4.4%, NNH=23 for 8 weeks. The Canadian Adverse Drug Reaction Monitoring program as of Sept 1999 has received 407 reports of which 256 were serious (64 convulsions, 52 psychiatric reactions and 128 allergic reactions including 14 cases of serum sickness)¹².

Dose and cost: 100 mg daily to 150 mg BID for depression. 150 mg daily for smoking cessation. Daily cost: \$0.53 - \$1.60.

Conclusion: Bupropion has antidepressant and smoking cessation effects through a unique mechanism of action. **The adverse effect profile is different from other antidepressants and includes convulsions and serious allergic reactions.**

This Letter contains an assessment and synthesis of published (and whenever possible peer-reviewed) publications up to June 1, 2000. 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 55 experts and primary care physicians in order to correct any identified shortcomings or inaccuracies and to ensure that the information is concise and relevant to clinicians.

New Data on Old Drugs

Doxazosin (Cardura[®]) arm terminated in RCT

Definition: ALLHAT is a large double blind RCT comparing four first-line drugs (chlorthalidone, 12.5-25 mg, doxazosin, 2-8 mg, lisinopril, and amlodipine) in patients > 55 yrs with elevated blood pressure and at least one other CHD risk factor. In January 2000, due to increased cardiovascular events, the doxazosin arm was terminated. The 3.3 year results of doxazosin versus chlorthalidone have been published¹³.

Evidence of effects on surrogate markers: Systolic BP was lower by 2-3 mmHg in patients receiving chlorthalidone. Total cholesterol and mean serum glucose were both lower by 0.2 mmol/L in the doxazosin group.

Morbidity and mortality: The primary outcome, fatal and non-fatal MI, was not different in the two groups, RR=1.03 (0.9-1.2). The secondary outcome, combined vascular disease, was significantly higher in the doxazosin group RR=1.25 (1.2-1.3), ARI=2.9%, NNH=34 in 3.3 years. This combined worse outcome was due to a significantly increased incidence of congestive heart failure, angina and stroke in patients randomized to doxazosin.

Conclusion: **Doxazosin and other alpha-blockers (terazosin, Hytrin[®] and prazosin, Minipress[®]) should not be used as first-line drugs in the management of elevated blood pressure.**

ARR=Absolute Risk Reduction, NNT=Number Needed to Treat to prevent one event, ARI=Absolute Risk Increase, NNH=Number Needed to cause one Harmful event

References

- Nolan JJ, Jones NP, Patwardhan R and Deacon LF. *Rosiglitazone taken once daily provides effective glycaemic control in patients with type 2 diabetes mellitus*. Diabet. Med. 2000;17: 287-294.
- Raskin P, Rappaport EB, Cole ST et al. *Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type II diabetes*. Diabetologia 2000;43:278-284.
- Fonseca V, Rosenstock J, Patwardhan R, Salzman A. *Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. A randomized controlled trial*. JAMA. 2000;283:1695-1702.
- Al-Saman J, Arjomand H, Kemp DG, Mittal M. *Hepatocellular injury in a patient receiving rosiglitazone. A case Report*. Ann Intern Med 2000; 132(2):121-4.
- Public Citizen Health Research Group. *Liver toxicity reported with the new diabetes drug rosiglitazone (Avandia)*. Worst Pills Best Pills News. 2000;6(4):25-26, 29.
- Drutz HP, Appell RA, Gleason D et al. *Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder*. Int Urogynecol J Pelvic Floor Dysfunct 1999;10:283-289.
- Abrams P, Freeman R, Anderström C and Mattiasson A. *Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder*. Br J Urol 1998;81:801-810.
- Reimherr FW, Cunningham LA, Batey SR, et al. *A multicenter evaluation of the efficacy and safety of 150 and 300 mg/d sustained-release bupropion tablets versus placebo in depressed outpatients*. Clin Ther 1998;20(3):505-516.
- Coleman CC, Cunningham LA, Foster VJ et al. *Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment*. Ann Clin Psychiatry 1999;11:205-15.
- Croft H, Settle E, Houser T et al. *A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline*. Clin Ther 1999;21(4):643-658.
- Hurt RD, Sachs DP, Glover ED et al. *A comparison of sustained-release bupropion and placebo for smoking cessation*. N Engl J Med 1998;337:1195-1202.
- Dunlop H. *Bupropion (Zyban, sustained-release tablets): update*. CMAJ 2000;162:106-107.
- The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. *Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone. The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT)*. JAMA. 2000;283:1967-1975.