Greetings to the 5th Annual Conference of the
Maine Benzodiazepine Study Group, October 2007

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It is a pleasure to send renewed greetings to the 5th Annual Conference of the MBSG.

A resounding success this year is the award of a $150,000 grant to the Maine Center on Aging from the U.S. Environmental Protection Agency for the launch of the first pharmaceuticals-return program to prevent discarded medications from polluting rivers, streams and groundwater. Warmest congratulations are due to Len Kaye, Stevan Gressitt, the study group consortium, and all others involved in implementing this plan. The program will make an important contribution to the environment and to the population in general. As far as I am aware, no similar scheme has been implemented in the UK. I hope efforts will be made to disseminate this plan nation-wide and worldwide.

An interesting observation to emerge from an early feedback about the pharmaceuticals-return program is that Klonopin was the most commonly returned controlled drug – a finding that renews the emphasis of the MBSG on benzodiazepines. Could it be that patients prescribed Klonopin are voting with their feet (or through their drainpipes) to register that they do not like this drug? It will be interesting to get the prescription figures for Klonopin in due course.

Judging from the e-mails I receive from the US, as well as a recent survey of benzodiazepine support groups,[1] Klonopin is the most widely prescribed benzodiazepine for anxiety in the US, followed by Xanax and Ativan. This trend is worrying as these potent drugs are often prescribed in excessive doses and for long periods – often years. Klonopin is also used, because of its relatively long half-life, as an aid in benzodiazepine withdrawal but is itself difficult to withdraw from, possibly because of its high potency and high binding affinity for benzodiazepine receptors. In the UK, Klonopin (called Rivotril) is only indicated for epilepsy but British physicians (since, like politicians, they tend to follow the US lead, as Blair followed Bush) are now prescribing it for anxiety disorders. I cannot help wondering whether the machinations of the pharmaceutical industry are currently designed to replace Xanax from the leading market share of benzodiazepines, just as Xanax pushed Valium from its leading position some years ago. The "Z-drugs" are climbing up the ladder too: I quite often hear of cases where Ambien (zolpidem) has been prescribed in addition to a benzodiazepines.

Another disquieting trend is the increasing prescription of new generation (atypical) antipsychotic drugs "off-label" for anxiety, insomnia and depression. These drugs, such as Seroquel (quetiapine), Zyprexa (olanzapine) and Risperdal (risperidone), are indicated for schizophrenia, mania and acute episodes in bipolar affective disorder, and have only been formally evaluated for these particular conditions. Yet surveys show that a high percentage of these drugs are prescribed off-label. For example, amongst 107,000 Medicaid patients in Georgia in 2001, 64% of antipsychotics were prescribed off-label, for conditions outside the approved indications[2]. Another report in 1998 found that 66.5% of patients collecting antipsychotic prescriptions at local pharmacies had been prescribed for off-label indications and were taking the drugs mainly as tranquillisers or anxiolytics[3]. In older patients (49-70

years) antipsychotics were almost exclusively used off-label. There has been no survey of the prescription of antipsychotics to patients taking benzodiazepines, but in my experience they are increasingly being prescribed for patients experiencing anxiety due to benzodiazepine tolerance after long-term use and for benzodiazepine withdrawal symptoms.

Some of these off-label prescriptions may be appropriate. However, atypical antipsychotics, though safer than the older ones, have potential adverse effects that are not seen with benzodiazepines including motor effects (extrapyramidal actions), tardive dyskinesia after long-term use and cardiovascular complications (hypotension and prolonged QT_c interval). They also have an abuse potential including use by "snorting" in prisons. In addition, they cause tolerance and withdrawal effects. A 3-year study of Seroquel in patients with schizophrenia and schizoaffective disorder showed therapeutic tolerance requiring escalation of dosage and withdrawal reactions including rebound psychosis[4]. No such study has been carried out in non-psychotic patients prescribed antipsychotics for off-label indications, including benzodiazepine dependence. A recent review of Seroquel for obsessive-compulsive disorder, personality disorder, post-traumatic stress disorder, anxiety, depression, and substance abuse suggests that it may be effective in these disorders in patients who do not respond to antidepressants and cognitive behavioural therapy[5]. Nevertheless, there have been so far no long-term studies in such patients and no investigations of withdrawal reactions which can include nausea, vomiting, and increased anxiety. (Studies of low dose Seroquel for these disorders including elderly patients and withdrawal reactions are currently under way in small numbers of patients.) Physicians prescribing these drugs off-label should be aware of these limitations and, as with all antipsychotics and benzodiazepines, should taper dosage gradually after long-term use.

Finally, despite concluding on a slightly disappointing note, I have to report the apparently low rate of nation-wide penetrance of the excellent "Guidelines for the Use of Benzodiazepines in Office Practice in the State of Maine" produced by Jim Berry and others in 2006. I understood that this had reached high governmental levels including the White House Office of National Drug Control Policy. But I have yet to find a physician or benzodiazepine support group outside the State of Maine who have ever heard of these evidence-based guidelines. Perhaps there are developments of which I am unaware….? The guidelines deserve to become a model for rational benzodiazepine prescribing and I hope that they, or a similar document, will soon be available in every general practitioner's and psychiatrist's office throughout the United States.

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References

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3. Hummer et al. Schizophrenia Research **29** (1) (1998)
4. Margolese et al. Journal of Clinical Psychopharmacol. **24** (1) (1998)
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