Drug company experts advised staff to withhold data about SSRI use in children

An internal document advised staff at the international drug giant GlaxoSmithKline (GSK) to withhold clinical trial findings in 1998 that indicated the antidepressant paroxetine (Paxil in North America and Seroxat in the UK) had no beneficial effect in treating adolescents.

Paroxetine is 1 of 6 drugs in the class of selective serotonin reuptake inhibitors (SSRIs) that Britain and the US have since banned for pediatric use because of increased risk of suicide. On Feb. 2, Health Canada issued a public warning that the pediatric use of 7 antidepressants — paroxetine, bupropion (Wellbutrin), citalopram (Celexa), fluvoxamine (Luvox), mirtazapine (Remeron), sertraline (Zoloft) and venlafaxine (Effexor) — should proceed only after consultation with the treating physician "to confirm that the benefits of the drug still outweigh its potential risks."

The GSK internal document obtained by *CMAJ* offers a glimpse into the inner workings of a drug giant. Entitled "Seroxat/Paxil Adolescent Depression: Position piece on the phase III clinical studies," the confidential document was prepared by the Central Medical Affairs team (CMAt), a division of SmithKline Beecham (which subsequently merged with Glaxo Wellcome to form GSK).

The document provides guidance on how to manage the results of 2 clinical trials conducted into the efficacy of paroxetine (Seroxat). Given that the clinical trials results were, according to the document, "insufficiently robust" to support an application to regulatory authorities for a label change approving Seroxat for use in pediatric depression, CMAt recommended the firm "effectively manage the dissemination of these data in order to minimize any potential negative commercial impact."

Sales for Seroxat amounted to almost $4.97 billion worldwide in 2003.

Study 329, conducted in the US from 1993–1996, was the largest trial to date on using an SSRI in a pediatric population. According to the document, the results indicated paroxetine was no more effective than placebo. In the other trial, Study 377, carried out in Europe, South America and elsewhere, placebo was actually more effective than the antidepressant.

The CMAt document advised that "Positive data from Study 329 will be published in abstract form at the [European College of Neuropsychopharmacology] meeting" in November 1998 and that "a full manuscript ... will be progressed." It also stated that "It would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine."

GSK spokeswoman Jill McKinlay-Morris said that "the memo draws an inappropriate conclusion and is not consistent with the facts." She didn't elaborate on that point, but went on to say "GSK abided by all regulatory requirements for submitting safety data. We also communicated safety and efficacy data to physicians through posters, abstracts, and other publications."

Study 329 was eventually published (*J Am Acad Child Adolesc Psychiatry* 2001;40[7]:762-72) in 2001. The authors concluded that paroxetine is "generally well tolerated and effective for major depression in adolescents." Among the 93 adolescents taking Seroxat, there were 5 serious cases of "emotional lability" (e.g., suicidal ideation/gestures). Among the 95 patients taking the comparison treatment, imipramine (Tofranil), there was 1 such case, and among the 89 subjects receiving placebo there was also 1. According to the article, only 1 serious adverse event — headache in 1 patient — was considered by the treating investigator to be related to paroxetine treatment.

Health Canada

A 1993–1996 industry study showed that paroxetine was no more effective than placebo in treating pediatric depression.

Britain's Medicines and Healthcare products Regulatory Authority (MHRA) advised doctors in June 2003 that paroxetine should not be prescribed to patients under the age of 18 because evidence from various clinical trials showed that episodes of suicidal behaviour were between 1.5 and 3.2 times higher in children taking the drug than in those receiving placebo. Several nations, including the US, France and Ireland, quickly followed suit.

The MHRA subsequently reviewed and banned the pediatric use of 6 other SSRIs (exempting fluoxetine [Prozac]) and is now reviewing their use among adults. The US Food and Drug Administration is now reviewing pediatric trials of 8 antidepressants. It's been estimated that as many as 11 million American, and 3 million Canadian children are taking antidepressants. — *Wayne Kondro*, Ottawa, and *Barbara Sibbald*, CMAJ

DOI:10.1053/cmaj.1040236