

## Appendix 2: Details of interrupted time-series analysis used to study the effect of 3 regulatory warnings on antipsychotic prescription rates among elderly patients with dementia

Segmented regression analysis of interrupted time-series studies<sup>1</sup> was used to identify the effects of the warnings. The dates of the warnings were used to divide the monthly data into 4 segments: 1) the pre-warning segment (May 2000 to September 2002); 2) the period after the first warning (October 2002 to February 2004); 3) the period after the second warning (March 2004 to May 2005); and 4) the period after the third warning (June 2005 to February 2007). A linear functional form that included an immediate effect on the level of utilization (i.e., intercept) and an ongoing effect on the change (i.e., slope) in utilization for each warning was specified.

More specifically the model took the form:

$$Y_t = \beta_0 + \beta_1 * T + \beta_2 * W1 + \beta_3 * TW1 + \beta_4 * W2 + \beta_5 * TW2 + \beta_6 * W3 + \beta_7 * TW3 + e_t$$

where  $Y_t$  is the utilization rate for the study drug at month  $t$  in the series;  $T$  is the time since the start of the observation period;  $W1$ ,  $W2$ ,  $W3$  are dummy variables equal to 0 before the first, second and third warning respectively and equal to 1 after;  $TW1$ ,  $TW2$ ,  $TW3$  are continuous variables equal to 0 before the first, second and third warning respectively and equal to the number of months after the corresponding warning; the error term ( $e_t$ ) consists of normally distributed random error and an error at time  $t$  that may be correlated to errors at preceding time points.

Coefficient  $\beta_0$  estimated the monthly prescription rate at baseline (May 2000);  $\beta_1$  estimated the baseline slope parameter representing change in prescription rate that occurred every month before the warning;  $\beta_2$ ,  $\beta_4$ ,  $\beta_6$  were changes in prescription rates immediately after the first, second and third warnings respectively compared with value from the end of preceding period (intercept changes);  $\beta_3$ ,  $\beta_5$ ,  $\beta_7$  estimated monthly change in prescription rates compared with trend before the warning (slope changes).

Antipsychotic prescription rates over time were tested and adjusted for dependent structure of the data. The regression model was first estimated on the entire series using the equation above. Resulting residuals were modelled on the entire series using an autoregressive moving average process.<sup>2-4</sup> Given the number of data points, the use of the entire period for the estimation process was justified.<sup>5</sup> It has been suggested that a segmented regression analysis include at least 12 data points before and after each intervention.<sup>1</sup> In this study, there were 29 data points before the first warning, and 17, 15 and 21 data points respectively after the first, second and third warnings.

A pure autoregressive process was used based on examination of autocorrelation, partial and inverse autocorrelation functions of residuals, the Durbin-Watson statistic, Akaike information criterion and Schwarz Bayesian criterion. Stationarity was checked using augmented Dickey-Fuller test. The presence of white noise was assessed using Liung-Box  $\chi^2$  statistic. Total  $R^2$  was at least 0.98 for all of the models, which indicated that the selected functional form and autocorrelation were able to account for a very large proportion of the variation in monthly prescribing rates.

The slope and intercept coefficients estimated from the models were used to assess the effects of the warnings.<sup>1</sup> Absolute and relative differences in antipsychotic prescription rates were estimated at 12 months after each warning. The absolute effect of each warning was measured as the difference between the estimated rates after the warning and the rates predicted from the structural part of the model in the absence of that warning (i.e., the rate predicted if the estimated slope and intercept term for that warning were set to zero). The relative effect of a warning was calculated as the ratio of absolute effect over the predicted rate as if the warning had not occurred. Confidence intervals around absolute changes were based on variance of sum of predicted and observed trends. Confidence intervals around relative changes were calculated using multivariable delta method for variance estimation.<sup>6</sup>

## References

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