EMISSION OF PHARMACEUTICALS IN THE ENVIRONMENT: AN IRISH PERSPECTIVE

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ABSTRACT

Emissions of pharmaceuticals for human use are influenced by trends in prescribing, trends in dosage strength and excretion rates of parent compounds or metabolites. Historical patterns of dispensing of pharmaceuticals in Ireland were analysed to generate forecasts of utilisation and identify substances displaying sharp consumption increases and therefore potential for cumulative occurrence in aquatic environments receiving wastewater effluents. Consumption trends were assessed fitting Holt-Winters filters to time series of dispensing data using R. Observations ranged between year 2008 and year 2013. The analyses provided linear and seasonal forecasts, delivering rapid prediction of monthly emission increases. Validation of the forecasts was achieved by means of training and test datasets. Using the criterion of at least 130% in percent increase of annual volume dispensed between year 2008 and year 2012 an initial formulary of 98 most frequently prescribed drugs in Ireland was reduced to 4 substances showing significant growth in utilisation, 2 antidiabetic drugs, pioglitazone (391.9%) and sitagliptin (330.9%) and 2 antiepileptic drugs, pregabalin, (134.1%) and levetiracetam (172.8%). Forecasts for September 2015 estimated the dispensing of pioglitazone at 1.64 kg/month and sitagliptin at 24.53 kg/month; trends of both substances were forecasted as stationary. Dispensing of pregabalin was forecasted to reach 280 kg/month with a monthly growth of 2.2 kg. Estimates of dispensing of levetiracetam suggested a volume of ~500 kg/month and a monthly increase of 3.86 kg by September 2015. Because of continuous emissions and resistance to wastewater treatment, some pharmaceuticals, for example pregabalin, have the potential to reach the aquatic environment in significant quantities. The environmental loading of pregabalin for Ireland was estimated to exceed 200 kg/month by September 2015. Emissions of pregabalin to wastewater are expected to continue increasing by ~1.63 kg/month, a current growth rate of ~10.0% per annum. Forecasts of pharmaceutical emissions can assist in prioritising scientific research in this growing source of emerging pollutants.

Keywords: Pharmaceuticals in the environment, pharmaceutical emissions, emerging pollutants.

1. Introduction

Research on pharmaceuticals in the environment is growing at a significant rate. Nikolaou *et al.* (2007) suggest that advances in analytical chemistry assisted the detection of ever lower trace levels of substances, enabling studies on pharmaceuticals in the environment. Kümmerer (2008) explains that although the body of knowledge on sources, occurrence, environmental fate and effect of these substances is expanding, understanding of the impacts remains limited. New drugs constitute a large proportion of pharmaceuticals with potential environmental impact (Dong *et al.*, 2013). Daughton (2014) identified 73 pharmaceuticals largely lacking environmental information in terms of occurrence, fate and effects. Daughton (2014) argues that, although these drugs are amongst the most frequently prescribed, research continues to focus on drugs of known occurrence. Petrovic (2014) reasons that selection of target analytes for new studies is primarily based on published results, causing a continuous neglect of environmental research of these emerging contaminants. Data on pharmaceutical sales are often employed in evaluations of risk

caused by concentrations of pharmaceuticals in the environment (Oosterhuis *et al.*, 2013; Verlicchi *et al.*, 2014). In fact market penetration is used to predict environmental concentrations submitted in dossier for marketing authorisation of new drugs in the European market (EMA, 2006).

The aim of this study was to identify pharmaceuticals utilised at substantially increasing rates. Using dispensing data, utilisation rates were calculated for 89 frequently prescribed pharmaceuticals in Ireland. Percent increase in annual dispensing over the period 2008-2012 assisted in selecting potential emerging pharmaceuticals in the environment. Four substances emerged as candidates for forecast of utilisation trends: pioglitazone, sitagliptin, levetiracetam and pregabalin. The selected substances were also identified in Daughton (2014) as lacking environmental information. Forecasts of dispensing were computed on the four substances fitting Holt-Winters filters to time series using R. Annual volumes of dispensing pioglitazone and sitagliptin expanded by 391.9% and 330.9% respectively between 2008 and 2012 and their current rate of dispensing were forecasted to be stationary. Levetiracetam and pregabalin increased respectively by 134.1% and 172.8%. The forecasted rate of increase of levetiracetam was 3.86 kg/month. Pregabalin was forecasted to increase at the current rate of 2.20 kg/month. The findings of this study warrant the necessity to widen the scope of research on pharmaceuticals in the environment to include emerging substances of limited environmental information.

2. Methods

Historical utilisation trends of pharmaceuticals in Ireland were evaluated using dispensing data provided by the Health Atlas Ireland. The data, covering the period from 1 February 2008 to 31 August 2013, are observations of pharmacy reimbursement claims representing the utilization pattern of ~73 % of the population. Annual volumes dispensed (kg) were calculated for 89 of the most frequently prescribed therapeutic drugs in Ireland and compiled into time series of monthly frequency. A percent increase >130% between year 2008 and year 2012 was used to identified drugs with high growth of utilisation. Trends and forecasts of utilization, generated fitting a Holt-Winters (HW) filter to time series using R, were computed for substances of high utilisation growth. HW forecasts return the traditional values of a linear equation, intercept (β_0) and slope (β_1), in the same units as the data, allowing for rapid evaluations. The amount dispensed on the initial month of the forecast is given by β_0 whereas the monthly change is derived from β_1. HW filters were applied to each dataset in linear mode, seasonal additive mode and seasonal multiplicative mode. HW filters were fitted to full time series of 67 months and to shortened versions of 59 months from February 2008 to December 2008. The latter time series functioned as training data for the performance evaluation of each filter mode against a test dataset from January 2013 to August 2013. The Mean Absolute Error (MAE) from an 8 month forecast generated with training datasets measured against test datasets determined the best performing HW method (Hyndman and Athanasopoulos, 2013). Forecast errors of the best fit to training data were analysed for evidence of autocorrelation, random variation and normality. Independence was tested using a correlogram and confirmed with a Ljung-Box Independence test. Normality was determined with a density plot and verified with the Shapiro-Wilk Normality test. The HW filter method providing the best Goodness of Fit (GoF) was fitted to full datasets from 1 February 2008 to 31 August 2013 to compute 25 month forecasts to September 2015.

3. Results

Percent increase between year 2008 and year 2012 of four candidate substances identified as drugs with high growth of utilisation is summarised in Table 1.1. While percent increase was significant for annual volume dispensed, evidence suggests that prescribed dosage follow a separate trend.

HW filters fitted in linear mode provided the best GoF for pioglitazone and sitagliptin forecasts whereas best results where attained fitting seasonal additive filters to levetiracetam and pregabalin forecasts (Figure 1.1). After a significant increase from 2008 to 2010, utilisation of pioglitrazone plateaued, resulting in a dispensed volume of 1.638 kg in September 2013.

Dispensing of sitagliptin followed a logarithmic growth curve declining gradually over the quinquennium. A total of 22.77 kg of sitagliptin were dispensed in September 2013.

Table 1.1.: Summary of Percent Increase (PI) of Annual Volume Dispensed (AVD) amd Average Daily Dose (ADD) between 2008 and 2012 for four pharmaceuticals identified as drugs with high growth of utilisation

Substance	ATC	AVD PI (%)	kg dispensed 2008	kg dispensed 2012	ADD PI (%)
Pioglitazone	A10BG03	391.9	4.09	20.12	7.9
Sitagliptin	A10BH01	330.9	62.7	270.2	-0.03
Levetiracetam	N03AX14	134.1	1767	4137	-2.7
Pregabalin	N03AX16	172.8	879	2398	-5.6

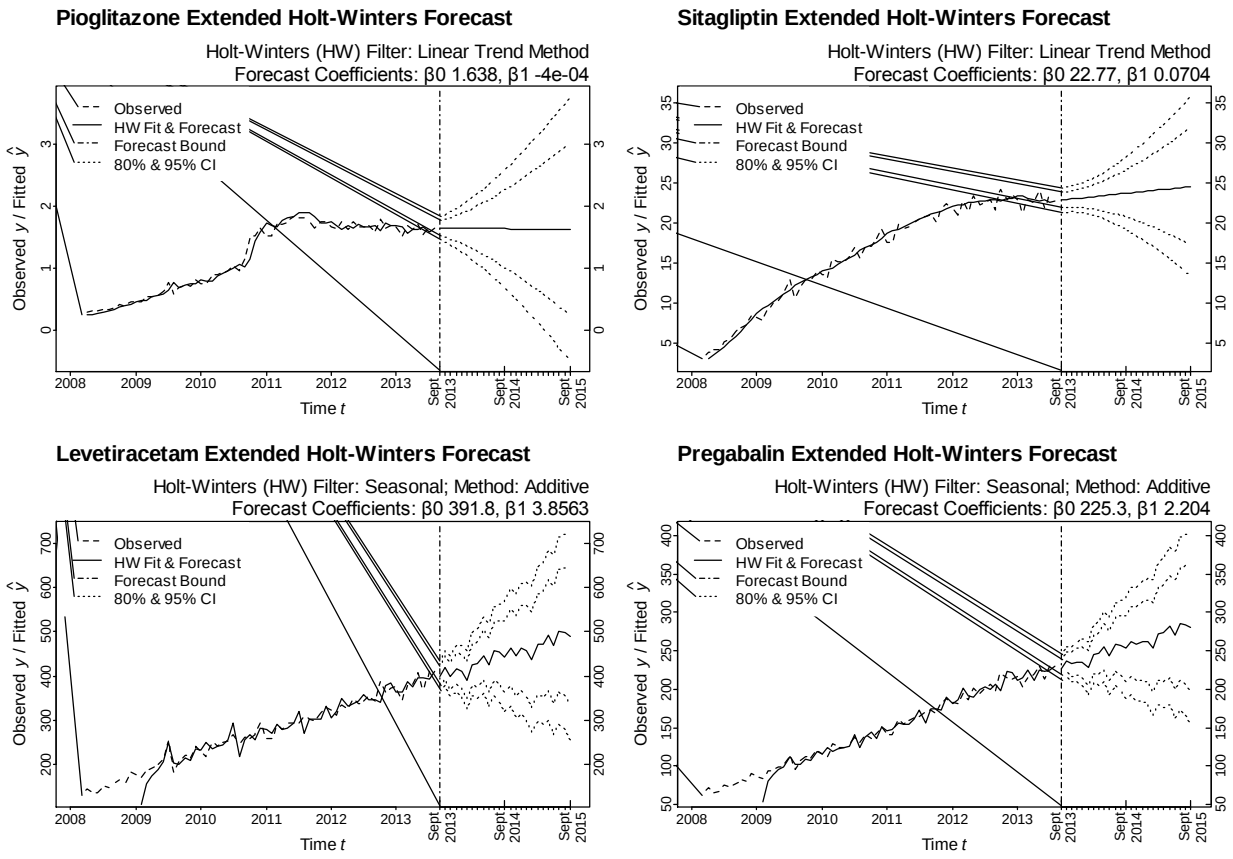

Figure 1.1.: Extended forecast to September 2015 of utilization trends of four pharmaceuticals identified as potential emerging contaminants.

Utilisation of levetiracetam and pregabalin followed a trend increasing linearly between 2008 and 2013. A total of 391.8 kg of levetiracetam and 225.3 kg of pregabalin were dispensed to the Irish population in September 2013. While pioglitazone accounted for the highest percent increase of volume dispensed annually between year 2008 and year 2012 (Table 1.1), extended forecasts to September 2015 suggested a stationary utilisation trend of the substance with a negligible decline of 0.0004 kg/month. Extended forecast of dispensing of sitagliptin indicated a weak rate of increase of 0.0704 kg/month. Projected dispensing for levetiracetam and pregabalin revealed a linear increase. Growth of use of levetiracetam was estimated at 3.8563 kg/month whereas utilisation of pregabalin was forecasted to increase at a rate of 2.204 kg/month.

According the HW forecast coefficients for pregabalin (Figure 1.1) utilisation of the compound for September 2015 was estimated at 280.4 kg. The pharmacokinetic excretion rate of pregabalin is 89% of the parent compound ingested whereas the wastewater removal rate of parent compound is reported at 82% (FDA/CDER, 2012). The environmental loading of pregabalin for September 2015 was therefore estimated at 204.6 kg/month. The monthly increase of 1.61 kg discharged to waterwater suggests a growth rate of ~10.0% of emission of pregabalin to the aquatic environment.

4. Discussion

Discovery and development of pharmaceuticals provide new therapeutic products which often displace the market penetration of a predecessor drugs (van der Aa *et al.*, 2011). However, because new environmental research on the effect of pharmaceuticals heavily relies on published data for the selection of target compounds (Petrovic, 2014), new drugs are systematically neglected in environmental studies. The four drugs identified by this research because of their significant increase in penetration of the Irish market are pioglitazone, sitagliptin, levetiracetam and pregabalin. Dispensing of antidiabetics pioglitazone and sitagliptin have increased significantly over the period of 2008 and 2012, however their current rate of utilisation was forecasted as stationary. Levetiracetam and pregabalin are classed as antiepileptics; their utilisation trends have been almost linear and predicted to continue increasing. The findings conform with steadily growing pharmaceutical sales observed in other countries (Bottoni *et al.*, 2010). The four drugs identified were all selected by Daughton (2014) as candidate orphaned chemicals for which environmental knowledge is lacking. However, while knowledge on their occurrence in the environment is limited, rates of pharmacokinetic excretion are readily available (Brayfield, 2014). Daughton (2014) argues that poor detection of some pharmaceuticals in the environment could be due to their intrinsic metabolism and suggests substances primarily excreted as parent compounds as better candidates for environmental research studies. Excretion rates of unchanged parent compound for the four candidate drugs are 15-30% for pioglitazone, 79% for sitagliptin, 66% for levetiracetam and 90% for pregabalabin (Brayfield, 2014). All fractions are excreted in urine. Although environmental information of these compounds is deficient, environmental hazard assessments are available. Ortiz de García *et al*. (2013) ranked pregabalin in fifth place amongst 98 compounds assessed for environmental hazard while pioglitazone and levetiracetam were ranked for prioritisation for research and decision making based on the US market (Dong *et al*., 2013). This study suggested that although prescribing frequency of the four substances evaluated increased significantly between 2008 and 2012, only levetiracetam and pregabalin are expected to continue to be dispensed at a growing rate. Unlike other pollutants pharmaceuticals are emitted continuously in the environment (Cooper *et al*., 2008) and many substances are resistant to wastewater treatment (van der Aa and Kommer, 2010). Performance of wastewater treatment installations also plays an important role in the removal of pharmaceuticals (BIO Intelligence Service, 2013). Pregabalin has a particular resistance to wastewater treatment and ~82% of the parent compound is estimated to reach treated effluent (FDA/CDER, 2012). With a forecasted environmental loading of ~204.6 kg/month for September 2015, and because of the high excretion rate of parent compound and resistance to wastewater treatment, pregabalin appears to be suitable candidate for future studies on occurrence and fate of pharmaceuticals in the environment.

5. Conclusions

The evidence provided by this study suggests that levetiracetam and pregabalin have the capacity to become emerging pharmaceuticals in the environment. Use of dispensing data can assist in rapid assessment and forecast of market penetration of substances, a key term in predicted environmental concentration calculations. Upcoming research should concentrate efforts on emerging pharmaceuticals in the environment to expand the current knowledge frontier. Ultimately, decision making processes ought to include emerging pharmaceuticals in future watch lists to provide comprehensive protection for the environment.

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