

# Ongoing initiatives within the Scottish National Health Service to affect the prescribing of SSRIs and their influence

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## Abstract

**Aim:** Increasing use of SSRIs in Scotland, coupled with safety concerns with some SSRIs, and the increasing availability of generic SSRIs, have resulted in multiple initiatives to improve the quality and efficiency of prescribing. Our aim is to assess their influence to provide future direction. **Materials & methods:** PCA database to document utilisation and expenditure on SSRIs between 2001 to 2017 and document initiatives. **Results:** Multiple interventions over the years increased INN prescribing up to 99.9% lowering overall costs. This coupled with initiatives to limit escitalopram prescribing due to concerns with its value resulted in a 73.7% reduction in SSRI expenditure between 2001 and 2017 despite a 2.34-fold increase in utilisation. Safety warnings resulted in a significant reduction in the prescribing of paroxetine, citalopram and escitalopram alongside a significant increase in sertraline **Conclusion:** Multiple initiatives have increased the quality and efficiency of SSRI prescribing in Scotland providing direction to others.

## 1. Introduction

Across countries, there has been considerable growth in the use of medicines. In part, this has been driven by aging populations, an increase in primary prevention strategies, as well as single disease model guidelines and policies [1,2]. We have also seen the continual launch of new high-priced medicines [2,3]. These factors combined are adding to resource pressures within countries resulting in models and initiatives to address this [2-5]. Scotland is no exception, and during the last 20 years or more there have been multiple initiatives to enhance the quality and efficiency of prescribing to help improve patient outcomes within finite resources providing direction to other countries.

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Initiatives include encouraging high rates of international non-proprietary name (INN) prescribing with generics typically seen as similar to the originator in all but a minority of situations [6-8]. This is important as there are still concerns with generics across a number of countries [9-11]. Savings once generics become available in Scotland are enhanced by their reduced costs, which can be as low as 3% of pre-patent loss originator prices [12,13]. INN prescribing is important in Scotland as pharmacists are not currently allowed to switch an originator or branded product to a generic if the physician prescribes the originator or branded product [7,14,15]. Alongside this, there have also been initiatives to increase the prescribing of multiple sourced products (generics) versus on-patent products in a class or related class where this does not compromise care to further save on costs. Classes include the proton pump inhibitors (PPIs), renin-angiotensin receptor blockers and statins [12,13,15].

Concomitant with this, there have also been multiple measures in Scotland to improve the quality of prescribing. These include encouraging physicians to prescribe higher doses of statins to improve long term outcomes as well as initiatives to reduce the prescribing of lipid lowering agents where there have been concerns with their effectiveness [12,15]. There have also been national and regional initiatives in Scotland to reduce the doses of PPIs prescribed, as well as encourage regular monitoring of patients on long-term PPIs, due to concerns with the consequences of their long term use [16-19].

Depression and other mental health conditions such as anxiety disorders are prevalent in Scotland with 11.3% of the adult population in 2010 to 2011 prescribed antidepressants [20]. These high rates of prescribing are possibly influenced by Westernised societies' expectations of happiness, and consequential medicalisation of unhappiness [21,22], as well as expansion of the indications for antidepressants. The selective serotonin re-uptake inhibitors (SSRIs) are the most frequently prescribed antidepressants in Scotland, accounting for over 50% of all antidepressants prescribed in recent years [20,23,24]. However, unlike the PPIs, renin-angiotensin blockers and statins, the situation with antidepressants is more challenging as they are not readily interchangeable, which limits the potential for therapeutic switching within a class [12,13,15,25,26]. This is because antidepressants such as the SSRIs exhibit subtle differences, which can affect both their efficacy and side-effects [27-29]. Having said this, there have been activities among the Health Boards (Regions) in Scotland to limit the prescribing of escitalopram versus other SSRIs, including fluoxetine and citalopram, where there have been considerable differences in costs but limited differences in patient outcomes [17, 30-32]. Health Board activities included prescribing targets for escitalopram [33]. They also include switching suitable patients prescribed escitalopram prior to citalopram to now being prescribed citalopram (C Johnson personal communication). Encouragingly, 90% of patients remained on citalopram after the switch at a three-month review. Such activities are important from a health policy perspective as they help to conserve resources without compromising care.

We have also seen initiatives in other countries to influence the prescribing of antidepressants where there have been concerns. This includes instigating prescribing restrictions for duloxetine in the management of patients with depression in Sweden due to concerns with its effectiveness and costs versus other antidepressants [34], as well as education and other activities to limit the prescribing of vortioxetine again due to concerns with its cost-effectiveness [35,36]. Such activities are likely to continue.

We are also aware that there have been concerns with the increased risk of suicides with paroxetine as well as other SSRIs since the early 2000s [37-42]. In addition, paroxetine is associated with a higher incidence of discontinuation symptoms versus other SSRIs, which necessitates a longer period of dose reduction [43]. There have also been concerns with potential QTc interval prolongation and Torsade de Pointes with citalopram and escitalopram from 2011 onwards [44], although the latter may be infrequently reported [45]. The concerns with possible QTc interval prolongation with citalopram and escitalopram resulted in the MHRA in the UK and Health Boards in Scotland providing guidance on their use [46-69]. This included recommending alternative SSRIs for new patients, as well as for patients where there were concerns with citalopram and escitalopram. This included sertraline with evidence of potential improved effectiveness and safety versus other SSRIs [48,50,51]. We are also aware that Health Boards in Scotland have also assessed factors associated with higher doses of SSRIs being prescribed [20,52]. Available evidence does not support the routine prescribing of higher

doses of SSRIs for the treatment of depression as this is known to increase anxiety, agitation and insomnia [53].

As a result of multiple activities in Scotland, rates of INN prescribing for the SSRIs were as high as 98% - 99% of their total utilisation in 2007 [13]. This coupled with initiatives to limit the prescribing of escitalopram versus citalopram resulted in expenditure on the SSRIs falling in Scotland by 59% between 2001 and 2007 despite a 2.37 fold increase in their utilisation [13]. This compares with appreciably increased expenditure for the SSRIs in Ireland (72% higher) and Portugal (93% higher) in 2008 and 2007 versus 2001 respectively where there were limited measures in both these countries to encourage the prescribing of lower costs multiple sourced SSRIs (generics) versus originators as well as on-patent escitalopram [13,54]. Such activities are important among high income countries with universal healthcare systems due to the continuous growth in the prescribing of medicines for patients with non-communicable diseases with ageing populations resulting in constant financial pressures, which is enhanced by the continual launch of new premium priced medicines to address areas of unmet need [2,4,55,56]. Obtaining low prices for good quality generics, and promoting their use, is also very important in low and middle income countries where access to medicines can be an issue with high patient co-payment levels [57,58]. Without such considerations, illness among family members can be potentially catastrophic for them [58,59]. Currently, fluoxetine is included in the WHO list of essential medicines [60].

Consequently, the objectives of this paper are multiple. Firstly, to assess the influence of the various multiple measures in Scotland on the overall volume and expenditure on the SSRIs in recent years, building on the earlier analysis [13]. Secondly, assess the extent of INN prescribing as well as the extent of price reductions for SSRIs following generic availability to help fund increased prescribing volumes without increasing costs, again building on the earlier analysis [13]. Thirdly, assess the extent of changes in the utilisation of citalopram, escitalopram, paroxetine and sertraline in recent years as a result of multiple initiatives and safety warnings. The findings will help guide future activities in Scotland as well as other countries, as all countries are looking to improve the quality and efficiency of their prescribing due to continuing pressures on resources.

We are also aware that there is a growing requirement for research evidence to guide future activities and initiatives to improve the selection, affordability, and rationality of prescribing of medicines for patients with mental disorders, which can be considered as public health psychopharmacology [61]. We hope our findings helps to start addressing this deficit.

## **2. Methodology**

### **2.1 Utilisation and expenditure data**

We used the prescription costs analysis (PCA) data in Scotland to analyse utilisation and expenditure data in ambulatory care [62]. PCA data is compiled by the Information Services Division (ISD) of NHS Scotland, which is an open source data set collecting data on the utilization and expenditure of medicines dispensed in community pharmacies in Scotland. The NHS in Scotland is a tax payer funded free at point of access health service, with currently no co-payment for medicines.

Information extracted from the PCA for each SSRI (N06AB – [63]) between 2001 and 2017 included: their generic name, commercial name(s), formulation(s), drug strength(s), number of dispensed units, cost per unit and total expenditure. The costs are in Great Britain pounds (GB£s) and include the gross ingredient costs (GIC) and cost per item for all SSRIs medicines dispensed during this period. No adjustment for inflation for prices was made, which is in line with previous studies, due typically to the rapid reduction in prices in the UK once originators become available as generics [12,13,64].

Whilst we are aware NHS Scotland routinely uses defined daily doses (DDDs) when presenting and discussing utilization data in line with international guidance [23,63,65] especially when different strengths are available such as citalopram (10mg, 20mg, 40mg) and sertraline (50mg, 100mg). However, we used items dispensed as we wanted to track this to reflect individual prescriptions, especially following changes in prescribing guidance, similar to the situation with lipid lowering agents and PPIs [15,19]. In the case of patients with chronic diseases such as depression, a prescription in terms of 'items dispensed' is usually for 28 or 56 days. However, as previously identified, there can be a tendency in recent years for physicians to increase the length of a prescription to help with their growing workloads [15].



## 2.2 Demand-side measures

As before, ongoing activities within the Health Boards and NHS Scotland to encourage INN prescribing as well as selected SSRIs have been collated using the 4E methodology: Education, Engineering, Economics and Enforcement [12,13,15,66]. Education refers to initiatives such as prescribing guidance and guidelines; engineering refers to organizational or managerial interventions such as prescribing targets; economics to financial incentives such as prescribing incentive schemes; and enforcement refers to regulations from health authorities [13,15,66]. However, the latter is rare in Scotland with no actual enforcement of regulations as seen for instance in Sweden with compulsory generic substitution and prescribing restrictions for statins in Finland and Norway following generic simvastatin [67-69].

We did not typically undertake any time-series analyses as multiple interventions inter-linked activities were undertaken at different times both nationally and regionally between 2001 and 2017. However, we did undertake such a time-series analysis comparing the changes in the items dispensed for citalopram and escitalopram before and after the warnings regarding possible QTc interval prolongation and any subsequent influence on the utilisation of recommended SSRIs such as sertraline [70]. A p value > 0.05 was seen as significant.

## 3. Results

### 3.1 Generic availability of SSRIs

Table 1 contains details of the year of patent expiry of the different SSRIs in Scotland.

Table 1 - SSRIs and their patent expiration date in Scotland from 2001 to 2017

Generic name	Commercial name (Originator)	ATC Code	Year of patent expiration
Fluvoxamine	Faverin®	N06AB08	Prior to 2000
Fluoxetine	Prozac®	N06AB03	2000
Paroxetine	Seroxat®	N06AB05	Prior to 2000
Citalopram	Cipromil®	N06AB04	2002
Sertraline	Lustrall®	N06AB06	2005
Escitalopram	Cipralex®	N06AB10	2014

### 3.2 Influence of multiple measures

A number of demand-side measures have been introduced nationally and regionally in Scotland in recent years to enhance INN prescribing as well as influence the prescribing of different SSRIs due either to concerns with their safety or value. These are summarised in Table 2.

Table 2 - Summary of principal demand-side measures introduced in Scotland between 2001 and 2017 that influenced SSRI utilization patterns [13,17,30,31,33,40,46,48,49,51,52,71-76]

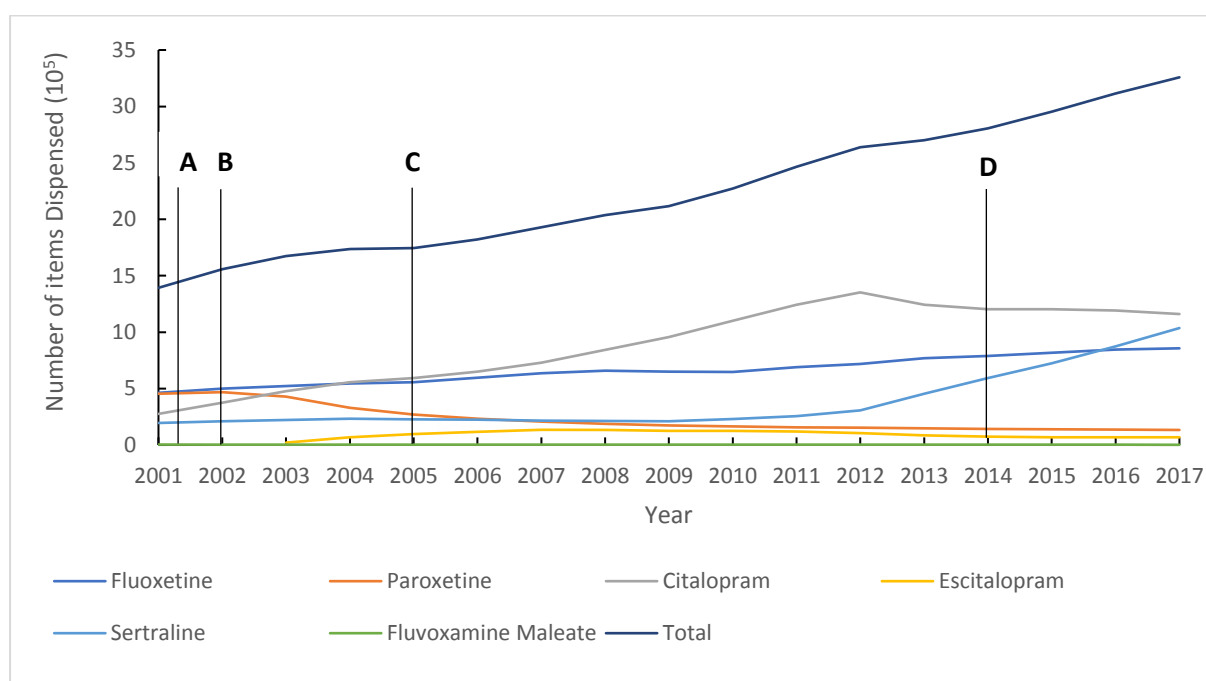
Measure	Year	National or Regional	Initiative
Education	2001 to 2017	National and Regional	<ul style="list-style-type: none"> <li>Physicians typically trained in medical school to prescribe by INN name with subsequent activities in GP practices coupled with IT systems to enhance INN prescribing</li> </ul>
	2003	National	<ul style="list-style-type: none"> <li>National warning regarding paroxetine in children</li> </ul>
	2003	Regional (Lothian)	<ul style="list-style-type: none"> <li>Lothian highlighting the extent of savings from the prescribing of generic paroxetine vs originator</li> </ul>
	2006	Regional (GGC)	<ul style="list-style-type: none"> <li>Fluoxetine and citalopram recommended SSRIs on the formulary list</li> </ul>
	2008 onwards	Regional (GGC)	<ul style="list-style-type: none"> <li>Educating GPs to regularly review patients on long-term antidepressants (doses prescribed, effectiveness, treatment duration, guideline improvements and costs)</li> </ul>
	2009	Regional (GGC)	<ul style="list-style-type: none"> <li>Fluoxetine and citalopram recommended SSRIs on the formulary list</li> </ul>
	2010	Regional (GGC)	<ul style="list-style-type: none"> <li>Sertraline added to the recommended formulary list of SSRIs</li> </ul>
	2009/10 to 2015	Regional (GGC)	<ul style="list-style-type: none"> <li>Review of patients receiving the same antidepressant for <math>\geq 2</math> years conducted among 180 GP practices involving &gt; 8000 patients, the majority of whom receive SSRIs</li> </ul>
	2011	National	<ul style="list-style-type: none"> <li>MHRA warning on QT interval prolongation with citalopram and escitalopram</li> </ul>
	2012 and 2015	Regional (GGC)	<ul style="list-style-type: none"> <li>Escitalopram and citalopram at high risk of QT prolongation</li> </ul>
	2012	Regional (Tayside)	<ul style="list-style-type: none"> <li>Warnings of QT interval prolongation with citalopram and escitalopram</li> </ul>
	2013	Regional (Lothian)	<ul style="list-style-type: none"> <li>Guidance on potential risks associated with the prolongation of QTc interval with different psychotropic medicines</li> </ul>
2017	NHS Grampian	<ul style="list-style-type: none"> <li>Fluoxetine and sertraline recommended SSRIs with sertraline recommended in patients with cardiovascular disease (caution with citalopram)</li> </ul>	
Engineering			<ul style="list-style-type: none"> <li></li> </ul>
	2002	National	<ul style="list-style-type: none"> <li>Audit Scotland benchmarking DDDs of non-fluoxetine SSRIs and the extent of INN prescribing across Scotland</li> </ul>
	2007	National	<ul style="list-style-type: none"> <li>Health improvement, Efficiency, Governance, Access to services and Treatment (HEAT) targets. NHS Boards to reduce the annual rate of increase of defined daily dose per capita of antidepressants to zero by 2009/10, and put in place the required support framework to achieve a 10% reduction in future years</li> </ul>
	2007/ 2008	Regional (Lothian)	<ul style="list-style-type: none"> <li>Total number of prescribed items of escitalopram <math>\leq 10\%</math> of all SSRIs (also linked with financial incentive schemes – Economics)</li> </ul>
	2008/09 to 2012/13	Regional (GGC)	<ul style="list-style-type: none"> <li>Fluoxetine &amp; citalopram as a % of all SSRIs, duloxetine, mirtazapine, reboxetine and venlafaxine items <math>\geq 65\%</math> (or an absolute increase of 5%) items and linked with prescribing financial incentives (Economics)</li> </ul>
2009/10	Regional (GGC)	<ul style="list-style-type: none"> <li>Escitalopram prescribing &lt;5% of all SSRIs items and linked to prescribing financial incentives (Economics)</li> <li>Fluoxetine 60mg capsules to 3x20mg capsules (GB£39/ patient as opposed to GB£360/patient)</li> </ul>	

			and linked to prescribing financial incentives (Economics)
	2011/2012	Regional (GGC)	<ul style="list-style-type: none"> <li>Citalopram and escitalopram QTc prolongation reviews of patients</li> </ul>
Economics (in addition to the above)	Ongoing	National/Regional	<ul style="list-style-type: none"> <li>Practice incentive schemes for reaching agreed prescribing targets</li> </ul>
Enforcement (although no actual enforcement in Scotland)	2002/ 2006	National	<ul style="list-style-type: none"> <li>Escitalopram initial rejected for use in NHS Scotland in 2002; however, accepted for use in 2006</li> </ul>

### 3.3 Total utilisation and expenditure

There was a steady increase in the number of total SSRI items dispensed between 2001 and 2017 (Figure 1).

Figure 1 – SSRI utilisation (items dispensed) in Scotland 2001 to 2017



NB: The solid lines indicate the time points where generics became available; [A] fluvoxamine, fluoxetine and paroxetine were already available by 2001; [B] generic citalopram; [C] generic sertraline; [D] generic escitalopram [D]

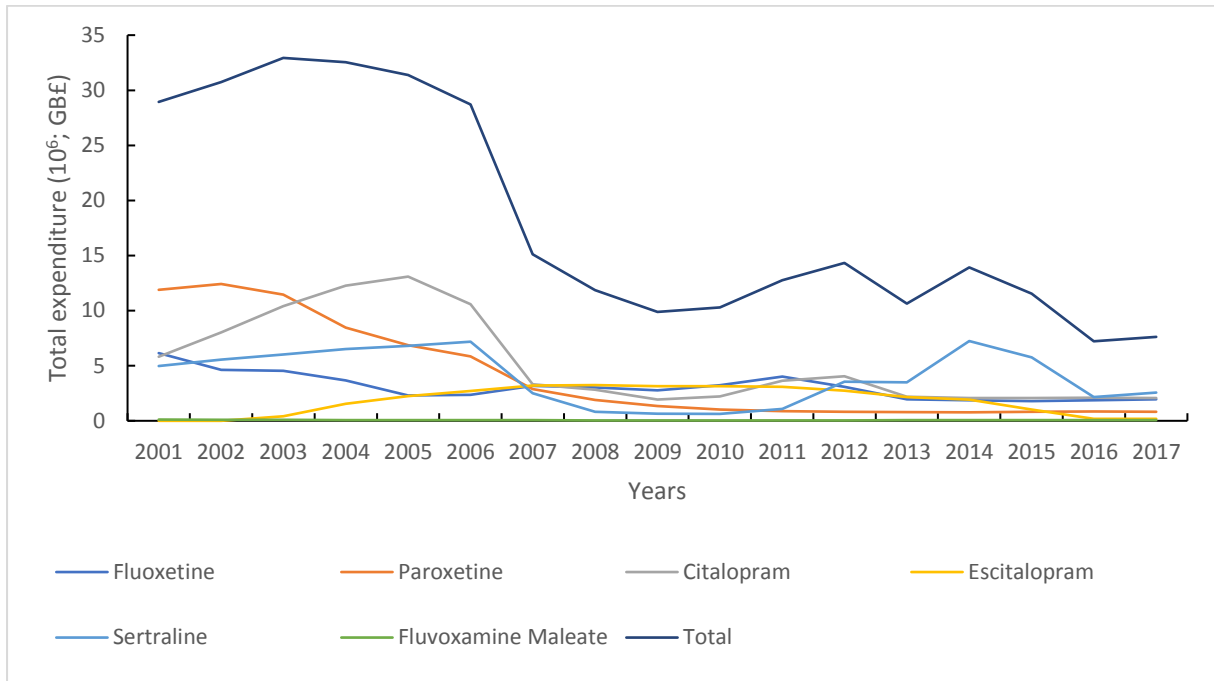
1.393 million items were dispensed in 2001 with a cost of GB£28.937 million, rising to 3.258 million items dispensed in 2017 at a cost of GB£7.613 million. This represents a 2.34-fold increase in SSRI utilisation during this period but a 73.7% reduction in expenditure.

The increase in SSRI utilisation during this period has been predominantly driven by increasing utilisation of citalopram, initially rising from 19.8% of total SSRI items dispensed in 2001 (276 thousand items) to 51.3% in 2012 (1.352 million items) before falling to 35.6% in 2017 following concerns with QT prolongation (Table 2). During this period, sertraline utilisation rose appreciably from 10.32% of total SSRI utilisation in 2011 to 31.8% in 2017. Concurrent with this, fluoxetine utilisation fell gradually from 33.2% of total SSRI items dispensed in 2001 to 26.3% in 2017 (Figure 1). The utilisation of paroxetine fell steadily throughout the study period from 32.7% of total utilisation in 2001 to 4.1% in 2017 following safety and other concerns, although these were not exclusively attributable to paroxetine. Overall during the study period, the number of items of paroxetine dispensed fell by 70.8%. There was low utilisation of escitalopram throughout the study period,

reaching a maximum of 6.99% of total items dispensed in 2007 before falling to 2.1% of total items dispensed in 2017 (Figure 1).

Figure 2 depicts a fall in total expenditure in recent years as more SSRIs lost their patent (Table 1).

**Figure 2 – Total expenditure on SSRIs in Scotland between 2001 and 2017**



This fall in SSRI expenditure was driven by a reduction in expenditure per item of the various SSRIs especially after generic availability (Figure 3), with Table 3 depicting the price reductions over time for each SSRI that had lost its patent during the study period, i.e. after 2001 (Table 1). Typically, the generic versions of SSRIs were dispensed once available with high rates of INN prescribing (Table 4).

**Figure 3 – Cost per item dispensed for the different SSRIs and total 2001 to 2017**

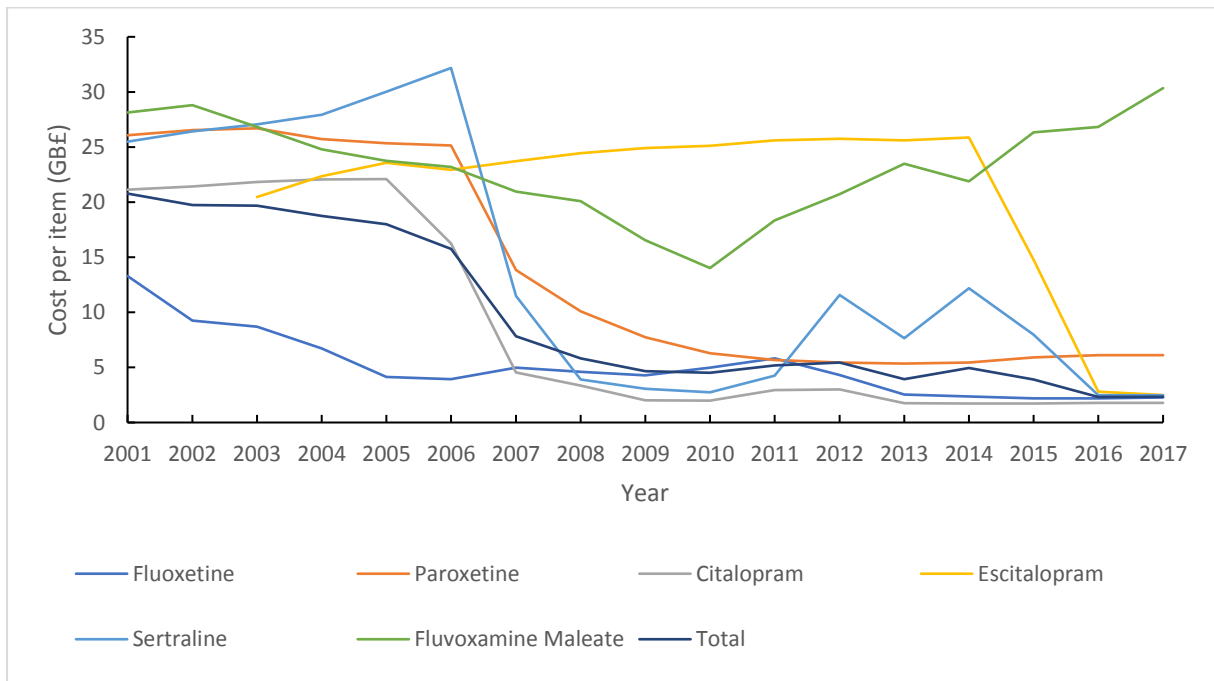




Table 3 – Price reduction in expenditure/ item dispensed for the various SSRIs in 2017 that had lost their patent after 2001 versus their prices just before patent loss

SSRI	% reduction in 2017
Citalopram	91.6
Sertraline	91.8
Escitalopram	90.4

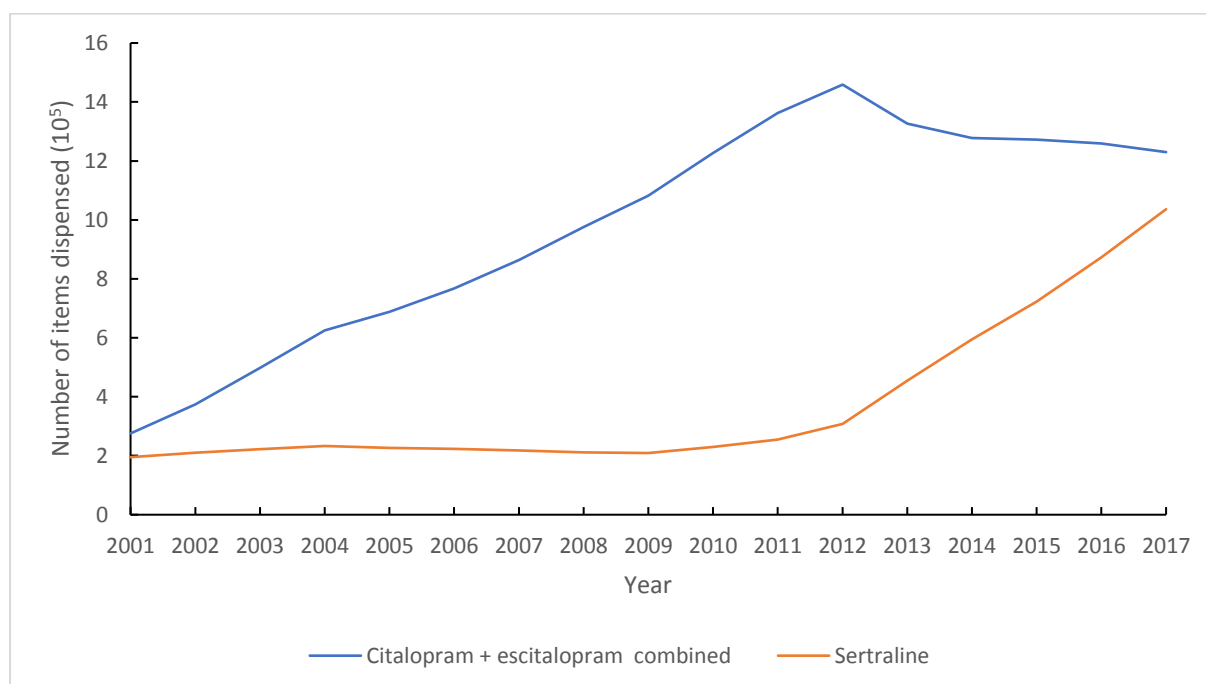
Table 4 – Rates of INN utilisation (items dispensed) of regularly prescribed SSRIs during the study period

SSRI	% INN (items dispensed)
Paroxetine	91.4% - 98.1%
Fluoxetine	98.7% - 99.7%
Citalopram	99.5% - 99.9%
Sertraline	98.5% - 99.7%

### 3.3 Differences in SSRI utilisation patterns before and after concerns with QT prolongation

Figure 4 depicts the changes in the utilisation (items dispensed) of citalopram, escitalopram and sertraline before and after concerns with potential QT prolongation with citalopram and escitalopram (Table 2), i.e. 2001 to 2011 and after 2012

Figure 4 – Extent of utilisation of citalopram, escitalopram and sertraline in Scotland 2001 to 2017



After the concerns with potential QT prolongation associated with citalopram and escitalopram use in 2012, there was a significant decreasing trend in citalopram and escitalopram use of 142,951 items/year ( $p < 0.001$ ) whilst the trend for prescribing of sertraline increased significantly by 141,016 items/year ( $p < 0.001$ ).

### Discussion

There has been an appreciable growth in SSRI items dispensed during the study period rising 2.34-fold (Figure 1). This may well be due to a widening of the indications for SSRIs to include anxiety as well as increasing diagnosis of depression as the diagnosis of depression and its management has now always been routinely recorded and coded as part of general practice contractual obligations

[20,77], and depression has been under-detected and under-treated. This may lead to under reporting of this common illness even when patients are now more likely to seek help for their emotional distress [78]. The recent mental health and wellbeing survey suggests that one in six adults in England have a common mental disorder, with more people now seeking treatment [79]. The survey data from England indicates there has been an increase in the proportion of people with clinical anxiety or depression disorders accessing mental health treatments, up from 24% in 2007 to 39% in 2014 [79]. There is no reason why Scotland should be any different from the findings in England. Patients are also receiving longer treatment [80]. Overall, we believe this growth in SSRI prescribing in Scotland in recent years (Figure 1) has been due to a combination of factors. These include SSRIs becoming available as low cost generics (Table 1, Figure 3), and adopted as first line agents for the treatment of depression combined with additional prescribing targets (Table 2); an increase in prevalence rates and patients accessing mental health services; increasing long-term use; a lack of a regular proactive review of patients when they are stable and not in crisis; and the routine use of higher SSRI doses, which is contrary to current guidelines and evidence [17,30,43,52,77-82].

The potential associated costs with this growth in SSRI utilisation have been offset by a considerable reduction in the cost/ item for the various SSRIs apart from fluvoxamine (Figure 3). The price reductions seen for the various SSRIs over time (Table 3) mirror those for the lipid lowering agents, losartan, PPIs and risperidone [15,19,83,84]. This coupled with high INN (Table 4) prescribing rates has resulted in an appreciable reduction in SSRI expenditure (73.7% reduction in 2017 versus 2001) to GB£7.613 million in 2017 (Figure 2). This is similar to the situation with lipid lowering agents and PPIs in Scotland [15,19] providing guidance to other countries struggling with resource pressures.

The high rate of INN prescribing for the SSRIs in Scotland as a result of multiple activities (Table 2) is also similar to the situation seen with generic PPIs, statins, renin-angiotensin drugs and anti-psychotics in Scotland [13,15,19,84,85]. This is encouraging and suggests no problems with the effectiveness and safety of generic SSRIs over many years. This is important for countries where there is still considerable prescribing of originator antidepressants despite the availability of good quality generics. This is not in the best interest of any key stakeholder group long term with potential resources being wasted, which could have been used to fund improved care in other situations including new medicines in patients with unmet need.

The reduction and then rise in the cost/ item for fluvoxamine (Figure 3) may be a reflection of its limited use (Figure 1); consequently, limited competition and need to reduce prices. This is seen in other situations across Europe [86]. However, this situation has made limited difference to the overall expenditure on SSRIs in Scotland with typically expenditure on fluvoxamine ranging from 0.21 to 0.85% of total SSRI expenditure during the study period.

The low utilisation of escitalopram in 2007 in Scotland at 6.99% of total SSRIs dispensed (7.0% DDD basis) and 6.51% in 2008 compares favourably with 17.3% in Portugal (DDD basis) in 2007 and 30.8% in Ireland in 2008 [13] following multiple initiatives (Table 2). This is the only example of generic availability (citalopram) influencing the prescribing of patented SSRIs (escitalopram). As mentioned, GPs certainly in Glasgow were encouraged to switch suitable patients who were prescribed escitalopram prior to citalopram to citalopram. This was seen as an effective measure to conserve resources without compromising care with, as mentioned, typically 90% of patients remaining on citalopram at the three-month review. Otherwise, there was no routine switching of SSRIs between patients. This was unlike the situation with the PPIs and statins in Scotland with no perceived differences in effectiveness between them [15,19]. Unlike the PPIs and statins, there were no national indicators encouraging the prescribing of particular SSRIs, although there were regional targets discouraging the prescribing of escitalopram (Table 2) [15,19,24]. This recognises the fact that patients being treated for depression are considered more vulnerable and therefore their medication once seen as effective and tolerated is typically not changed. In addition, antidepressants certainly initially are prescribed as courses rather than life-long chronic treatment; consequently, a change to a different SSRI was generally through trying to influence the initial prescription rather than switching patients once prescribed a particular SSRI (Table 2). The situation with escitalopram was different (Table 2) as there was perceived limited clinical differences with citalopram; however, considerable differences in costs once generic citalopram became available (Figure 3).

The utilisation patterns for paroxetine (Figure 1) were in line with expectations following the safety warnings; however, these were not exclusive to paroxetine although paroxetine was singled out

initially [37,38,41]. In addition, concerns with the need for lengthier dose reductions following the decision to stop prescribing [43].

The significant reduction in the utilisation of citalopram and escitalopram, coupled with significantly increased use of sertraline in recent years, is also encouraging following safety warnings (Table 2, Figure 4). This further illustrates the favourable influence of both national and regional initiatives on effecting physician prescribing habits, which is not always the case [87-89]. As a result, again providing guidance to other countries.

### **Limitations**

We are aware of a number of limitations with this study. This includes the fact that we were only able to analyse prescriptions dispensed and not their indication. However, two large studies in one Scottish Health Board area indicating that 87% of antidepressants were prescribed for depression, and less than 3% were prescribed for non-licensed indications [20,77]. We could also not analyse the strength of doses prescribed to ascertain whether there were any change in the doses of SSRIs prescribed although two regional Scottish studies indicate that higher SSRI doses are possibly being prescribed more commonly [20,78]. We are aware that there are multiple factors which are associated with prescribing of higher SSRI doses including which anxiety disorders are being treated. For depression, which general practice a patient attends, if they are prescribed an SSRI for two years or more, and if they are co-prescribed benzodiazepines and/or z-hypnotics for more than 8 weeks [20]. We also did not analyse utilisation in terms of DDDs, which would have been more sensitive to changes in the doses of SSRIs prescribed; however, such studies have been undertaken. We could also not assess patient outcomes with the changes in SSRI prescribing patterns. Finally, from a safety perspective assessing the impact of the MHRA warning on the incidence of QTc prolongation and sudden cardiac death is very challenging as QT prolongation as a cause of death cannot be confirmed at autopsy. From an efficacy and wellness perspective, there are challenges with routinely collecting for patient-level outcome data in ambulatory care for common mental health problems; consequently, limiting a national assessment of the impact of SSRI prescribing. Despite these limitations, we believe our findings are robust and provide guidance for the future.

### **Conclusion**

The considerable reduction in the cost of SSRIs over the years once generics became available has resulted in lower costs despite an appreciable increase in SSRI utilisation. This is to the benefit of all key stakeholders since the savings can be used in other disease areas such as funding new medicines that address current unmet need within a resource constrained environment.

Overall, the loss of patents has not influenced SSRI prescribing patterns apart from escitalopram. This is unlike the situation seen with the PPIs and lipid lowering medicines, and reflects the differences in the effectiveness and safety of the different SSRIs.

The changes in the prescribing patterns of paroxetine, citalopram and escitalopram are encouraging and shows healthcare professionals in Scotland act quickly on safety and other warnings, providing an example to other countries.

Finally, we believe analyses such as this as part of public health psychopharmacology are justified and provide practical research findings to guide future care. Consequently, we see this discipline growing in the future.

### **Summary points**

- There is increasing use of antidepressants including SSRIs in Scotland in recent years with expanding of indications, greater awareness and medicalisation of depression, and greater number of patients accessing treatment for their depression
- There have also been safety concerns with some SSRIs including initially paroxetine and subsequently citalopram and escitalopram
- The increasing availability of generic SSRIs, the need to conserve costs including limiting prescribing of patented escitalopram, and safety concerns has resulted in multiple initiatives in Scotland in recent years

- High INN prescribing (up to 99.9%) and generics up to 92% below originator prices, coupled with initiatives to limit escitalopram prescribing, resulted in a 73.7% reduction in SSRI expenditure between 2001 and 2017 despite a 2.34-fold increase in utilisation
- The safety warnings resulted in a significant reduction in the prescribing of paroxetine, citalopram and escitalopram coupled with a significant increase in the prescribing of sertraline
- Overall the multiple initiatives have increased the quality and efficiency of prescribing

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### Conflicts of interest

Chris Johnson, Marion Bennie, Simon Hurding, and Sean Macbride Stewart are all employed by NHS Scotland. The authors have no other conflicts of interest to declare.

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'\*' – of interest, or "\*\*\*" – of considerable interest

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