RESEARCH ARTICLE

# Generic atypical antipsychotic drugs in Belgium: their influence and implications

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**Introduction:** Generic atypical antipsychotic drugs should be a focus of attention given their expenditure. However, there is a recognized need to tailor treatments. There were no specific measures in Belgium to enhance the prescribing of oral risperidone following generics in January 2008. Prescribing restrictions have remained for long-acting risperidone injections throughout. **Objective:** Assess changes in risperidone utilization before and after oral generics were reimbursed, as well as the utilization and expenditure of the various risperidone preparations. **Method:** Principally a retrospective observational study and interrupted time series design. **Results:** As expected, no increased utilization of oral risperidone after generics. Both originator and generic oral risperidone prescribed, with the originator reducing its price. Generic risperidone was 59% below prepatent loss prices by September 2012. **Conclusion:** Authorities cannot rely on a 'spill over' of learning from other disease areas to affect changes in physician prescribing habits. Specific measures are needed to encourage generic risperidone where appropriate. However, their influence will be limited by the complexity of the disease area.

antipsychotics ▪ Belgium ▪ demand-side measures drug utilization ▪ generics

Pharmaceutical expenditure has risen by more than 50% in real terms among Organisation for Economic Cooperation and Development countries between 2000 and 2009 [101], resulting in pharmaceutical expenditure typically the largest cost component of ambulatory care expenditure [1–4]. European countries have instigated multiple measures to try and address this to maintain the European ideals of comprehensive and equitable healthcare. Policies and initiatives for established drugs include measures to increase the utilization of generics at low prices versus originators and patented products in a class or related classes where all drugs are seen as similar for all or nearly all patients [1,2,4–6].

Belgium has introduced multiple reforms and initiatives in recent years, details of which are described elsewhere [7–11]. The principal supply-side measure to lower prices of generics and originators once multiple sources are available is the reference price system (Anatomical Therapeutic Classification Level 5 [102]). Under this system, the manufacturers of generic drugs have to lower their prices to at least the reference price to be reimbursed (16% reduction vs prepatent loss prices until 2002, 20% until 2003, 26% until 2005 and currently 31%). The manufacturers of the originators typically lower their prices to similar levels to ensure some utilization as patients are required to pay the price difference for a more expensive product than the current reference priced product. This strategy is undertaken by originator manufacturers as generic substitution is currently not allowed in Belgium when originators are prescribed apart from antibiotics and antimycotics where substitution has been compulsory with the cheapest product since May 2012, and patients seek to reduce their copayment levels. Reducing the price of originators to at or near the reference price enhances their utilization. Demand-side measures are principally targeted at physicians who recognize that reference pricing for

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the molecule is also a demand-side measure. They include participation in local quality meetings, provision of guidelines and encouraging international nonproprietary name (INN) prescribing, as well as monitoring their prescribing of low-cost medicines against agreed targets. Low-cost medicines are defined as generics prescribed by INN or originator medicines whose prices have dropped to the current reference price for the molecule. Agreed quotas (targets) for all medicines dispensed in the community were 49% for psychiatrists and 42% for neuropsychiatrists in 2011. Initiatives also include prescribing restrictions for the class or drugs within a class (Anatomical Therapeutic Classification Level 4) [10]. There are currently few incentives for pharmacists to dispense generic medicines and, as mentioned, generic substitution is currently not allowed in Belgium apart from antibiotics and antimycotics.

Atypical antipsychotic drugs (AAPs) are a potential target for health authority and health insurance company activities across Europe, with worldwide sales over US$5 billion per year in the early 2000s, reaching US$14.6 billion in the USA alone in 2009 [12–14]. In addition, medicine costs can be an appreciable component of the overall costs of treating patients with schizophrenia since psychopharmacologic drugs represent the backbone of treatment [15–18].

However, there have been concerns about the quality of the evidence suggesting greater health gain with the atypical versus typical antipsychotic drugs, alongside concerns over a greater level of side effects, such as weight gain, hyperlipidemia and Type 2 diabetes, with AAPs [12,19–22,103]. In addition, the risk of QT prolongation and subsequent arrhythmia-related events – that is, Torsade de pointes and sudden cardiac death – have been seen as increasingly important when physicians are deliberating over which AAP to prescribe [23,24]. In the past, AAPs have been perceived as generally having a more favorable cardiac safety profile. However, this is changing with recent studies, including case series studies and pharmacovigilance analyses, showing similar reporting ratios between typical and AAPs in clinical practice [25–29]. Recent studies have also shown that the highest risk of mortality among patients with schizophrenia is now from quetiapine, and the lowest from clozapine [30].

These debates have continued with the publication of the CATIE study, which showed limited differences in the overall effectiveness between the various antipsychotic drugs, although the study is not without criticism [12,31–33]. However, there is considerable variation in the effectiveness of the different antipsychotic medicines between individual patients, as well as differences in the side effects between different antipsychotic medications [22]. Consequently, the authors recommended that treatments for schizophrenia should be individualized [22].

However, other authors believe that the modest health gains with AAPs that have been reported do not adequately reflect the improvements in the quality of life perceived by patients, clinicians or carers [34]. This is leading to their increasing use in recent years, which is likely to continue [35–37,104].

Consequently, the availability of generic AAPs should be welcomed by the authorities in Belgium to save costs. However, it is recognized that schizophrenia and bipolar disorders are complex diseases to treat compared with, for instance, acid-related stomach disorders or hypercholesterolemia. In addition, AAPs cannot be considered to be a single class in view of the heterogeneity of their pharmacological activities. This is unlike the situation for proton pump inhibitors (PPIs) or statins [4–6,11]. As a result, there is a greater necessity to tailor treatments to the individual patient, for example, olanzapine should not be considered in young women with weight problems and risperidone should not be considered in patients with sexual problems. In addition, switching patients between different antipsychotic drugs should never be considered if their condition is stable. This is unlike the situation seen with statins or renin-angiotensin inhibitor drugs [4,38–41].

The principal objective of this paper is to assess the changes in the utilization patterns for risperidone and other AAPs in Belgium before and after oral risperidone was included in the reference price system (January 2008). We would not expect any significant changes in the utilization of risperidone versus patented AAPs in the absence of any specific demand-side measures, apart from continued prescribing restrictions for long-acting risperidone injections (LARI) and the continued quotas for the prescribing of low-cost medicines described earlier. This is similar to the findings in other European countries [42,43]. However, we would expect to see a growth in the utilization of oral generic risperidone and a corresponding decline in the utilization of the originator. However, we would expect this growth to be moderated by the extent of any price difference between the originator and

the generic. This is unlike the rapid uptake of generics in the UK once available, with high voluntary INN prescribing rates [4,5,42]. We would also expect to see a reduction in the utilization of LARIs following the introduction of stricter conditions, which is similar to the situation seen with statins and renin-angiotensin inhibitor drugs [4,5,44]. Under the prescribing restrictions for LARIs (Chapter IV medicine – a 'chapter IV' medicine can only be prescribed subject to prior approval from the advising physician of the patient's health insurance fund; otherwise a 100% patient copayment applies. A chapter I medicine can be prescribed without restrictions) [10] during most of the study period [105,106]:

- LARIs are reimbursed if administered for maintenance of schizophrenia in patients who are already being treated with antipsychotic medications and in whom therapy with an antipsychotic is long term and there are concerns with compliance. Otherwise 100% co-payment;
- The reimbursable dosage is limited to two administrations per month for Risperdal® Consta®;
- Reimbursement may be granted without the approval of the medical officer unless the words 'not reimbursable' are written on the prescription. Under these conditions, pharmacists may apply third-party payment principals.
- The prescriber must be in possession of a report prepared by a physician specialized in psychiatry or neuropsychiatry that shows that the patient was in the situation referred to in the first bullet point at the beginning of the therapy by the concerned specialty. Upon request, the prescriber must provide these data to the medical adviser, who is a physician appointed by the insurer of the patient.
- Simultaneous reimbursement of different LARIs is not allowed.

However since July 2012, following the completion of the principal study, there has been greater scrutiny concerning prescribing requests for LARIs, which was part of general measures to conserve resources. If the report of the (neuro) psychiatrist is either not available, or its content does not satisfy the controlling physician from the insurer, the health insurance physician can request more evidence from the prescriber or the (neuro)psychiatrist who initiated the treatment. Reimbursement is denied if the controlling physician is not satisfied with the data provided.

Second, this article assesses the actual changes in the prices for the various risperidone preparations after risperidone was included in the reference price system and compare these with expectations. Third, we suggest additional measures that could potentially be introduced in Belgium to further enhance the prescribing of first-line generic AAPs where pertinent.

## Methods

This is principally a retrospective observational study. We used an interrupted time series design to analyze the changes in monthly reimbursed prescriptions of all patients in Belgium covered by the social health insurance system who were prescribed at least one AAP (N05AH03 to 05, N05AL05, N05AX08, 12, 13) [102] between January 2006 – that is, 23 months before risperidone was included in the reference price system (January 2008) – and August 2011 – that is, 43 months after. Zotepine (N05AX11) is not present in Belgium. These time periods were chosen as this study was part of a much larger cross national comparative study.

Clozapine was not included as this is reserved for refractory patients given its side-effect profile [45–47,104]. The principal data source was Pharmanet [107]. This database contains all reimbursed medicines dispensed in public pharmacies in Belgium, regardless of the specialty of the prescriber, that are reimbursed by the National Institute for Health and Disability Insurance through the third payer system. Its completeness for antipsychotic drugs is enhanced by the fact that in Belgium all health insurance is compulsory, all antipsychotics are reimbursed and all community pharmacies work with the third payer system.

The IFSTAT database was also used to assess the utilization and expenditure patterns for the various risperidone preparations up to September 2012. This is because we wanted more up-to-date figures for the various risperidone preparations including preliminary trends in the utilization of LARIs following the tightening of the regulations in July 2012. This database is managed by the Institute for Pharmaco-Epidemiology in Belgium. This Institute is a joint initiative by the Association of Pharmacists in Belgium (APB), which represents the independent community pharmacies, the Organisation of the Cooperative Community Pharmacies and several organizations of medical doctors. The data collected in IFSTAT is

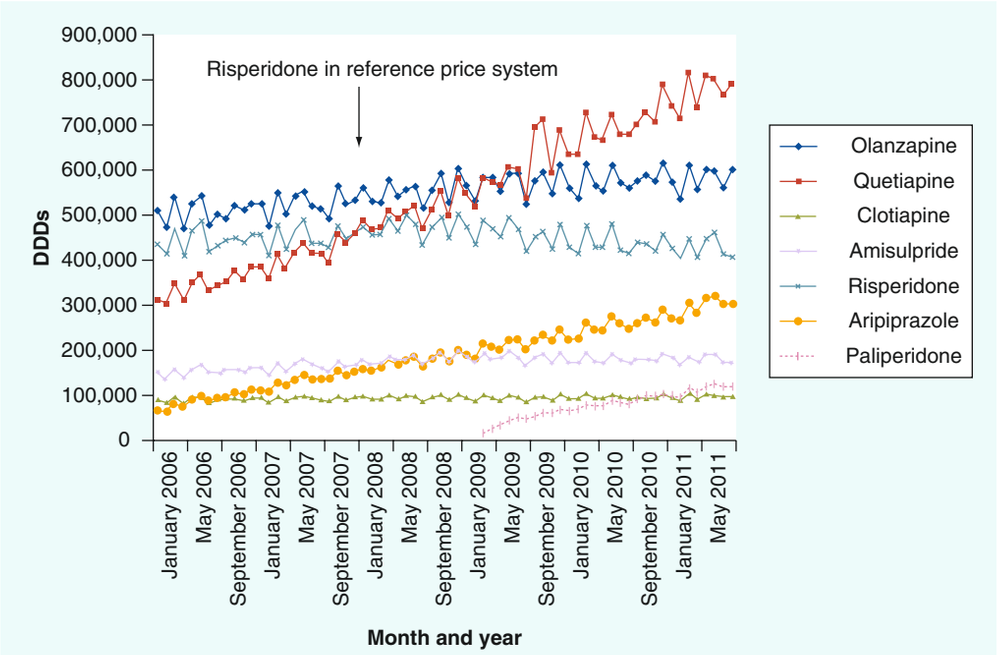


**Figure 1. Utilization of different atypical antipsychotic drugs from January 2006 to August 2011 (defined daily doses).**
DDD: Defined daily dose

also a subset of the Pharmanet data. However, no personal data are collected and the data collected are restricted to the invoicing offices from members of the APB or Organisation of the Cooperative Community Pharmacies. Having said this, IFSTAT contains 93.3% of the National Institute for Health and Disability Insurance expenses for medicines delivered in Belgian community pharmacies. Consequently, it is an accurate reflection of the situation in Belgium. No time series analyses were undertaken for the LARIs as there were insufficient time periods after July 2012.

The utilization of atypical antipsychotics was assessed using defined daily doses (DDDs). DDDs are defined as "the average maintenance dose of a drug when used in its major indication in adults" [108]. We used this measure as DDDs are recognized as the international standard to assess utilization patterns within and between countries [48,49,108]. 2011 DDDs were used in line with international guidance [108,48,49]. Expenditure/DDD was also calculated for the various risperidone preparations from January 2006 to September 2012 using the IFSTAT database to assess the influence of the inclusion of oral risperidone in the reference price system on subsequent price reductions.

Serial autocorrelations of risperidone DDDs were assessed in the interrupted time series design using an ARIMA model and a Box-Jenkins-Tiao strategy [50]. DDDs were plotted over time in months. The graphs were visually inspected to assess the trends or the nonstationarity of the data. Alongside this, a segmented regression analysis of the interrupted time series was used to assess the effect of the inclusion of risperidone in the reference pricing system from January 2008 onwards. Common segmented regression models were used to fit a least-squares regression line to each segment of the independent variable (time $t$), assuming a linear relationship between time and the outcome within each segment. The effect of the intervention was assessed using the model: $Y_t = \beta_0 + \beta_1 (\text{time}_{t = 0, 1, 2, \ldots 68}) + \beta_2$ (intervention 1$t$) + $\beta_3$ (time after intervention 1 $t$) +$e_t$, and so on,where $Y_t$ was risperidone DDDs per month $t$, time is a continuous variable indicating time (in months) at time $t$ from the start until the end of the observation period, intervention is an indicator variable for time $t$ occurring before ($t$ = 0 month) or after ($t$ = 1 month) the inclusion of risperidone in the reference price system, and $e_t$ is the error term at time $t$ [51]. The Durbin-Watson statistic was calculated to test for a serial autocorrelation of the error terms in the regression models [52]. The statistical package IBM SPSS Statistics version 19.0 was used for

all analyses. A p-value of <0.05 was considered significant [53].

## Results

There appeared to be limited change in the utilization of risperidone before and after the inclusion of oral risperidone in the reference price system (Figure 1).

If anything, there appeared to be a decline in the monthly utilization of risperidone versus the other selected AAPs following the inclusion of risperidone in the reference price system from January 2008 onwards (Figure 2). Alongside this, there was a continued growth in the utilization of the other selected AAPs (Figure 2).

As a result, the utilization of risperidone as a percentage of total AAPs decreased from 28% of total AAPs in early 2006 to 17% by August 2011.

This fall in the utilization of risperidone postgenerics bordered on significance (Table 1).

The decline in the utilization of risperidone in recent years is opposite to the growing utilization of quetiapine (reimbursed in 2002), aripiprazole (reimbursed in 2005) and paliperidone (reimbursed in 2009) (Figure 1).

Both originator and generic oral risperidone are being prescribed (Figure 3), with a growing utilization of LARIs until recently (Figure 3).

Overall, both general practitioners and psychiatrists are involved with the prescribing of risperidone, with the rates remaining relatively constant throughout the study period (Figure 4).

There was a decline in expenditure/DDD for both the originator and generic oral risperidone over time (Figure 5). Expenditure/DDD for oral generic risperidone was €1.31/DDD by September 2012 (Figure 5), 59% below prepatent loss originator prices at €3.21.

Reimbursed expenditure/DDD for both oral risperidone preparations were appreciably lower than that for LARIs at €9.381 in September 2012 (Figure 4). However, this was lower than €11.06 in March 2012 just before a 15.5% price reduction [De Bruyn K, Pers. Comm.]:

- Risperdal Consta 50 mg intramuscular 1 × 50 mg plus 2 ml solvent: ex-factory price of €146.94 from April 2012 (€173.89 before)
- Risperdal Consta 37.5 mg intramuscular 1 × 37.5 mg plus 2 ml solvent: ex-factory price of €123.98 from April 2012 (€146.72 before)
- Risperdal Consta 25 mg intramuscular 1 × 25 mg plus 2 ml solvent: ex-factory price of €91.83 from April 2012 (€108.68 before)

This price reduction was part of a general 1.95% price reduction instigated nationally by the National Institute for Health and Disability Insurance in April 2012 to reduce pharmaceutical expenditure [106]. However, pharmaceutical companies were free to apply this reduction in any way they wished across their portfolio. Hence, there has been a greater price reduction for LARIs. This price difference between risperidone preparations resulted in LARIs contributing 60–68% of total expenditure on risperidone in recent years (Figure 4) despite its limited utilization (Figure 3).

## Discussion

As expected, there was no increase in the utilization of risperidone following its inclusion in the reference price system (Figures 1 & 2); in fact the reverse is true (Table 1). This suggests no increasing use of risperidone in new patients where indicated in the absence of therapeutic switching among patients. However, we cannot say this with certainty without analyzing patient data. These findings are similar to those from other European countries [42,43,54]. This may reflect the advice from organizations such as NICE in the UK that treatment should be individualized [103].

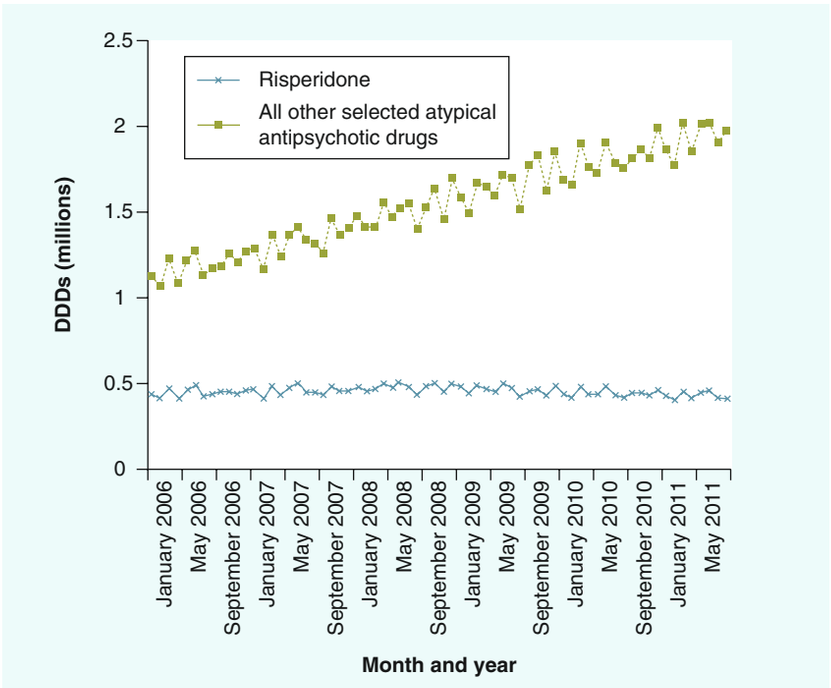


**Figure 2. Monthly utilization of risperidone and other selected atypical antipsychotics before and after the inclusion of risperidone in the reference price system (January 2008) in defined daily dose (millions).**
DDD: Defined daily dose.

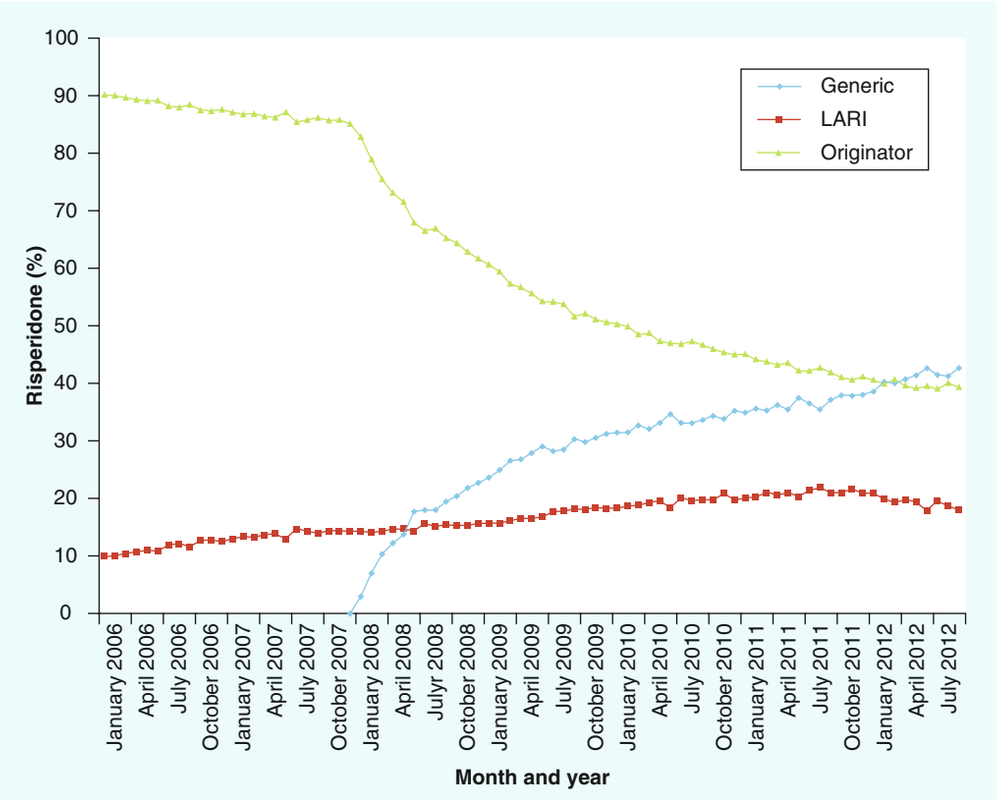


**Figure 3. Utilization of different risperidone preparations as a percentage of total risperidone (defined daily doses) January 2006 to September 2012.**
LARI: Long-acting risperidone injections.

In addition, the conclusions from various published studies that treatment with AAPs should be tailored to individual patients in view of differences in side effects between treatments, as well as considerable differences in their effectiveness between patients [22,30,55,56]. Having said this, there was growing utilization of patented AAPs during the study period (Figure 1). This may reflect the marketing activities of the patented manufacturers influencing the choice of AAP [42,109–111]. However, this remains to be proven.

This is unlike the situation with PPIs, statins or renin-angiotensin inhibitor drugs in Belgium where there was increasing use of generics versus patented products in the class following multiple demand-side measures [10,11,57]. This suggests that there is no 'spill over' or crossover of learning in practice from one disease area to another to effect changes in physician prescribing habits. Consequently, physicians may not necessarily think of prescribing a generic AAP first-line where pertinent unless there are specific measures

**Table 1. Parameter estimates, standard errors and p-values from the segmented regression model predicting the extent of risperidone defined daily doses before and after oral generic risperidone was reimbursed (coefficient variable is risperidone items dispensed in defined daily doses).**

| Model | Unstandardized coefficients | | Standardized coefficients | T | Significance* | 95% CI for B | |
|---|---|---|---|---|---|---|---|
| | *B* | *Standard error* | β | | | *Lower bound* | *Upper bound* |
| Time | 767.79 | 688.01 | 0.561 | 1.12 | 0.269 | -606.67 | 2142.25 |
| Reimbursement | 25,890.09 | 11,683.22 | 0.461 | 2.22 | 0.030 | 2550.17 | 49,230.01 |

*Significance at $p < 0.05$.
Dependent variable: risperidone defined daily doses.

encouraging this. This is no doubt exacerbated on this occasion by the recognized need to tailor treatment in patients with schizophrenia or bipolar disease, as well as no desire among physicians to switch treatments when patients are stable on a particular AAP.

Specific demand-side measures could include new guidance and guidelines highlighting the preferential prescribing of generic AAPs first-line where there are no pertinent patient issues. This could be followed-up with discussions at quality meetings. However, it is recognized that the influence of any such activities may well be reduced by the need to tailor treatments to individual patients. Other measures could include changing the reimbursement status of oral patented AAPs to Chapter IV, while moving generic atypical drugs to Chapter I. This mirrors the situation of LARIs in Belgium [105]. However, this may not be necessary with both generic olanzapine and generic quetiapine now available in Belgium, which were the two most prescribed AAPs (Figure 1). Such measures may also be difficult to implement in patients with schizophrenia given the need to tailor treatments for this patient population. The tightening of reimbursement criteria for LARIs in July 2012 and its influence (Figure 3) [105] further reduces the need for additional measures. We believe that the tightening of regulations surrounding the reimbursement of LARIs in July 2012 helped to continue its reduced utilization from 113,937 DDDs in September 2011 to 99,280 in June 2012 and 87,278 in September 2012. However, we cannot say this with certainty until we perform a more thorough analysis. We also believe that the utilization of LARIs will fall further with the new regulations, building on the reductions seen soon after the implementation of stricter guidelines in July 2012. As a result, resources will be conserved further. If substantiated with a more thorough analysis, these findings will mirror those of the PPIs, statins and renin-angiotensin inhibitor drugs that greater scrutiny of prescribing restrictions further limits subsequent prescribing [4,5,44]. Again, providing guidance for other situations and countries where health authority personnel are seeking additional

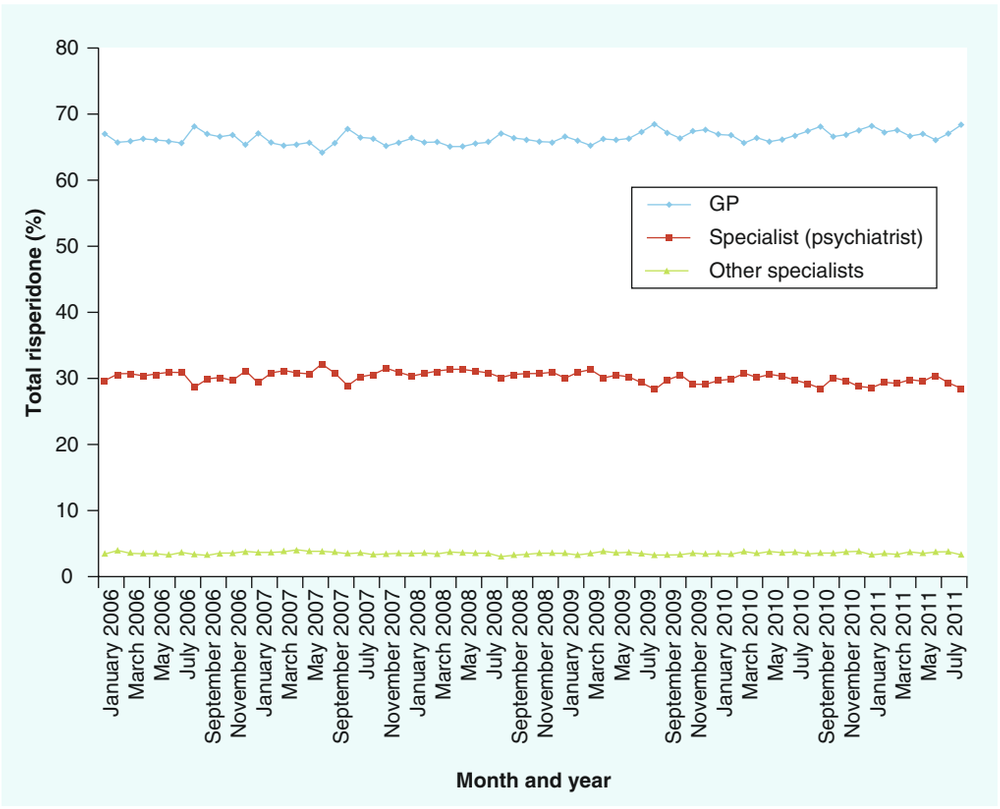


**Figure 4. Prescribing of risperidone by speciality (defined daily doses basis) during the study period.**
GP: General practitioner.

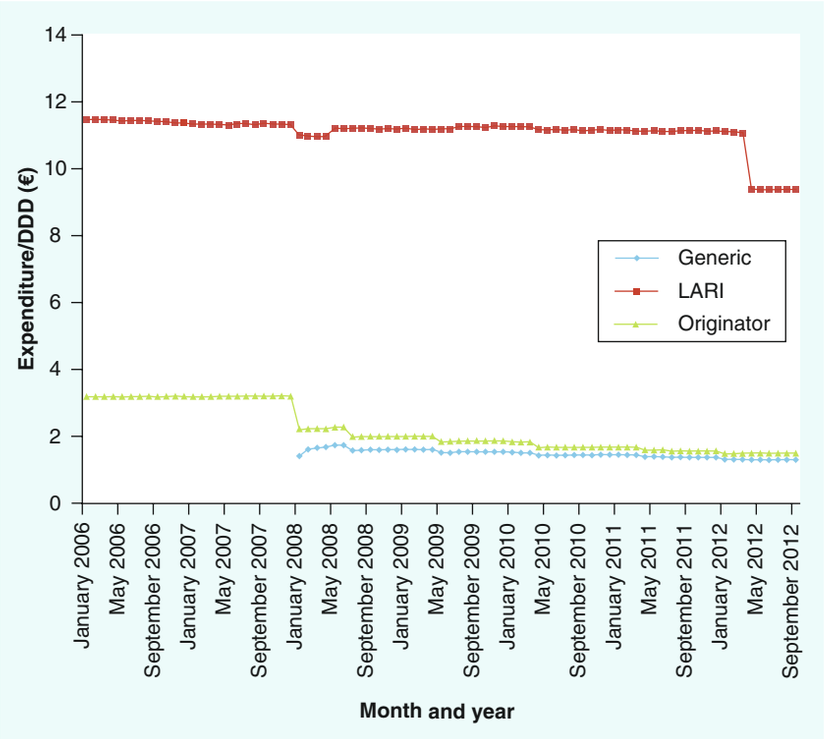


**Figure 5. Expenditure/defined daily doses for the different risperidone preparations January 2006 to September 2012.**
DDD: Defined daily dose; LARI: Long-acting risperidone injections.

measures to further enhance the rational use of their medicines.

The reduction in expenditure/DDD for both generic and originator oral risperidone (Figure 5) is in line with expectations based on the current regulations. As a result, there is slower conversion from the originator to generics compared with countries with aggressive demand-side measures, such as Sweden with compulsory generic substitution or the UK with high voluntary INN prescribing [39,42]. In the UK, risperidone was already 92% generic (on a DDD basis) within a short time after its availability [38,42], In addition, generic risperidone was only 16–20% of prepatent loss prices in Sweden and the UK at similar time periods [39,42]. We believe that the authorities in Belgium could learn from the experiences in Sweden and the UK.

We are aware of a number of limitations with this study. This includes no access to patient data to assess whether there has been an increase in the prescribing of risperidone since the availability of generics. However, the continued decline in the utilization of risperidone coupled with increased utilization of patented AAPs suggests that this will not be the case. We have also used two sources of data for the reasons described. However, they are closely related. Lastly, we have not fully explored the influence of tighter prescribing restrictions for LARIs. This will be explored in future studies.

## Conclusion & future perspective

Specific measures are needed to encourage the prescribing of generic first-line AAPs when multiple choices are available and appropriate. Authorities cannot rely on the transfer of learning regarding the prescribing of generics from other classes to affect changes in prescribing habits. This is similar to the findings when losartan recently lost its patent. Again, multiple measures were needed to enhance its utilization versus patented angiotensin receptor blockers; otherwise there was limited change in its subsequent utilization [10,58–60]. We believe that this is an important finding for health authority and health insurance company personnel as they consider future initiatives to further conserve resources to help fund increased volumes and new premium priced drugs.

Specific measures could include guidelines coupled with greater discussions in quality meetings and/or changes in the reimbursement status of patented drugs. However, their impact will be influenced by the complexity of the disease area and the need to tailor treatments. Specific measures could also include prescribing restrictions for oral patented AAP, building on those for LARIs.

However, we do not believe that the authorities in Belgium are planning any additional measures. This is because more oral AAPs are now available as multiple sourced products and there is greater scrutiny over the prescribing and reimbursement of LARIs. However, this may change following the launch of new premium priced AAPs.

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## Executive summary

- Atypical antipsychotic drugs (AAPs) should be a focus of health authority activities in view of their considerable expenditure worldwide.
- However, reforms and initiatives are difficult to implement in view of the recognized need to tailor treatments to the individual based on their characteristics. In addition, AAPs should not be considered as a single class and patients should not be switched between treatments if they are responding to a particular AAP.
- Consequently, the availability of generic risperidone should be welcomed to help conserve resources.
- No specific demand-side measures were instigated by the authorities in Belgium to enhance the prescribing of oral risperidone first-line where pertinent. However, there were continued restrictions on the prescribing of long-acting risperidone injections throughout the study period.
- As a result, there were no changes in the utilization of risperidone postgenerics, mirroring the findings from other European countries. If anything, there has been an appreciable fall. As a result, authorities need to instigate specific measures to influence physician prescribing habits and cannot rely on a 'spill over' effect, considering the difficulties with this particular patient population.
- There was a gradual increase in the prescribing of generic versus originator risperidone over time reflecting reducing costs of the originator. By September, expenditure/DDD for generic risperidone was 56% below prepatent loss originator prices.
- Further restrictions were introduced for long-acting risperidone injections after the principal study had ended. Early analysis suggests that this has had an influence on their subsequent use. However, further analyses are needed before any definitive statements can be made.

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