and 0.2 ml of saline). The following substances were administered intragastrically 2 times a day at 7-hour intervals for 30 days starting from the 1st day of EAE induction: anti-S100 (n = 20, 2.5 mL/kg/d); distilled water (control; n = 20, 5 mL/kg/d). Reference drug (Glatiramer acetate, Copaxone®, Teva, Israel, n = 20) was administered intramuscularly (4 mg/kg) from the 2nd to the 25th day after EAE induction.

Results: The severity of neurologic symptoms was assessed in points: muscle weakness, tremor (0.5 point); resistant paresis (1 point); paralysis (1.5 points). Clinical Index (CI) was calculated as a sum of the symptoms for 4 limbs. CI was defined as zero if visible clinical signs were absent, and as 6 in case of animal's death. Cumulative index for each rat was calculated as a sum of individual CI for the total disease period (30 days). Time to disease onset (days) and the mean severity of the disease (points) were recorded in each group.

The key results of the study are presented in the **Table**.

	Groups, the number of animals	Proportion of Animals With Symptoms	Severity of Symptoms	Time to Disease Onset, days	Mean Cumulative CI, Points (M ± m)	
		Mild, %	Average, %	Severe %		
Control, n = 20	80	20	25	35	9.5 (8.0–11.3)	27.53 ± 7.19
Glatiramer acetate, n = 20	65	5	40	20	10.0 (9.0–11.0)	18.03 ± 6.20
Anti-S100, n = 20	85	40	40	5*	12.0 (8.0–14.0)	18.96 ± 5.94

*The difference with control is significant at $P < 0.05$ (chi-square test).

Conclusion: Anti-S100 ameliorated clinical symptoms of EAE in Wistar rats: they both significantly reduced the severity of the disease and delayed the disease onset. The results give promise to patients in a search of a treatment option for multiple sclerosis.

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PP261—UTILIZATION OF TRIPTANES IN SWEDEN; ANALYSES OF OVER THE COUNTER AND PRESCRIPTIONS SALES

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Introduction: In Sweden, some triptans became available over the counter (OTC) in 2008. The present study describes the utilization pattern of prescribed and OTC triptans in Sweden over time.

Patients (or Materials) and Methods: Wholesaler and aggregated sales data from the National Corporation of Swedish Pharmacies between 1991 and 2006, and patient identity data on dispensed prescriptions between 2006 and 2010 from the National Prescribed Drug Register were used to investigate volume and expenditure of triptans over time. Prevalence was calculated for 2007 and 2011, measured as the number of patients/1000 inhabitants dispensed at least 1 triptan prescription. To illustrate proportions of patients dispensed large and small amounts of the drug, respectively, Lorentz percentiles and Lorentz curves were used. Analyses were done by age and gender.

Results: Volumes of triptans sold has increased continuously to 7.0 million defined daily doses (DDD) dispensed on prescriptions and 0.7 million DDDs OTCin 2011. The prevalence of triptan utilization was 10.0 in 2007 and increased slightly to 10.1 in 2011. A marked gender difference was found with a 3.6 times higher prevalence of triptan use in women both years. The mean number of DDD increased with 10%, from 67 DDD per patient in 2007 to 74 DDD per patient in 2011. The median volume per patient increased even more, 20%, from 30 DDD per patient in 2007 to 36 DDD per patient in 2011. Dispensed triptans were unevenly distributed within the population. In 2007, in women, 46% of the volume was purchased by 10% of those consuming the largest amounts. In men, the corresponding proportion consumed by 10% heavy users was 50%.

Conclusion: Triptans OTC has increased since the introduction as has the purchases of prescribed triptans. The number of patients dispensed triptans on prescription remained stable during the period studied even though the volumes increased.

Disclosure of Interest: None declared.

PP262—CAN AUTHORITIES TAKE FULL ADVANTAGE OF THE AVAILABILITY OF GENERIC ATYPICAL ANTIPSYCHOTIC DRUGS? IMPLICATIONS FOR THE FUTURE

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Introduction: There could be an opportunity for health authorities to take advantage of oral generic atypical antipsychotic drugs (AAPs) given their considerable expenditure across countries. However, schizophrenia and bipolar disorders (BPD) are complex to treat, with the need to tailor treatments. Consequently, there is a need to assess changes in risperidone utilization before and after oral generic risperidone was reimbursed among European countries, as well as the utilization of generic versus originator risperidone, to provide future guidance.

Patients (or Materials) and Methods: We principally used an interrupted time series design of monthly aggregated AAP utilization (2011 DDDs) up to 2 years before generic risperidone became available and reimbursed and up to 6 years after in Austria, Belgium, Ireland (GMS population), Scotland, Spain (Catalonia), and Sweden; (ii) Demand-side measures captured and categorised using the 4Es (Education, Engineering, Economics and Enforcement). Expenditure was also measured. Only administrative databases were used.

Results: There were generally no specific measures among the various authorities to preferentially encourage the prescribing of oral

generic risperidone, although there were prescribing restrictions for long-acting injectable risperidone in Austria and Belgium. As a result, no change in its utilization after generics reimbursed. Overall, high utilization of generic versus originator risperidone once available. Appreciable reduction in the price of generic risperidone once it became available limited the extent of any subsequent increase in AAP expenditure despite increasing utilization.

Conclusion: No apparent effectiveness or safety problems with generic risperidone. Authorities cannot rely on a spillover effect from other disease areas to change physician prescribing habits, exacerbated on this occasion by the need to tailor treatment approaches with different AAPs having different mechanisms of action and appreciable variability in their effectiveness and side-effects between patients Consequently, specific demand-side measures are needed to encourage the prescribing of generic AAPs first line where appropriate, exacerbated by the complexity of these disease areas. Likely in any event that there will be limited influence of any measures in changing subsequent physician prescribing habits when managing patients with schizophrenia or BPD compared with acid-related stomach disorders or hypercholesterolemia as a greater need to tailor treatments. Generally no specific measures planned by these authorities to influence future prescribing habits with further generic AAPs becoming available.

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PP263—IMPORTANCE OF TDM, PHENOTYPING AND GENOTYPING DURING INTOXICATION WITH VENLAFAXINE

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Introduction: Antidepressive drug venlafaxine belongs to the serotonine and norepinephrine reuptake inhibitors. It is primary metabolized by CYP2D6 to its active metabolite O-desmethylvenlafaxine and by CYP3A4 to N-desmethylvenlafaxine. The range 0.3-5.2 for O-desmethylvenlafaxine/venlafaxine ratio was estimated for extensive and intermediate metabolizers.

Patients (or Materials) and Methods: There is described intoxication of woman (41 years) treated by combination therapy venlafaxine 150 mg/d, mianserine 60 mg/d, clonazepam 1 mg/d, and olanzapine 10 mg/d. TDM of these substances was provided using LC-MS/MS method to estimate phenotype of venlafaxine and to compare with genotype.

Results: On admission, toxic plasma level of venlafaxine was found (2638 ng/mL) and after reduction of the dose to 75 mg/d plasma level was estimated in therapeutic range (364 ng/mL). The ratio O-desmethylvenlafaxine/venlafaxine was estimated between 0.005 and 0.016 showing poor metabolizator. Genetic examination detected homozygotes deletion of the gene CYP2D6 *5/*5 and explained phenotype. Plasma level of olanazapine was found in therapeutic range, plasma level of clonazepam was found below therapeutic range.

Conclusion: The ratio of the metabolite to the parent substance (phenotype) allows us to detect any deviation in the metabolism of drugs which can be subsequently explained by determination of genotype. Therapeutic drug monitoring contributes to the optimalization of pharmacotherapy in the case of psychotropic drugs.

Disclosure of Interest: None declared.

PP264—4-METHYLESCULETIN A DUAL ACTING INHIBITOR OF ACETYLCHOLINESTERASE AND XANTHINE OXIDASE

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Introduction: Alzheimer's disease is a neurodegenerative disorder associated with depletion of acetylcholine in neuronal terminals with increased oxidative stress in cells resulting in neuroinflammation. Inhibiting acetylcholine esterase (AchE) increases the concentration of neuronal acetylcholine. Further xanthine oxidase (XO) is an important source of free radicals and plays an important role in oxidative stress associated with neuroinflammation. Thus, a dual acting inhibitor of AchE & XO can be a good candidate for the treatment of neurodegenerative disorders like Alzheimer's. The aim of this study is to explore the inhibitory potential of 4-methyl esculetin against both AchE and XO.

Patients (or Materials) and Methods: The X-ray crystal structures of rivastigmine bound to acetylcholinesterase (AChE) (PDB 1GQR) and quercetin bound to xanthine oxidase (XO) (PBD 3NVY) were obtained from the Protein Data Bank. The proteins were prepared for the docking studies with the Protein Preparation Wizard in the Schrödinger Suite 2012 (Schrödinger LLC, USA). The ligand 4-methyl esculetin (4-ME) was docked into the target proteins AhcE and XO and binding poses ranked by Glide Score (SP). The inhibitory activity of 4-ME towards AchE was measured by an in vitro assay using rat brain AchE, and inhibition of XO was done using crude XO obtained from rat liver tissue.

Results: The docking studies revealed that 4-methyl esculetin binds in a similar fashion to both AChE and XO and makes identical interactions as the native ligands (rivastigmine for AchE & quercetin for XO). The Glide Score for 4-methyl esculetin (–6.97 for AchE and –7.78 for XO) also does not differ significantly in both targets; hence, it can be said with confidence that 4-ME should exhibit comparable potency towards the 2 protein targets. This is well substantiated by in vitro enzyme assays that confirmed the equal inhibitory properties of 4-ME towards both the target *viz.* AchE and XO. Kinetic studies showed that 4-ME acts as a competitive inhibitor against XO while exhibiting mixed type inhibition toward AchE.

Conclusion: The results of the present study indicate that a combination of both AchE and XO inhibitory properties for 4-ME could make it a useful asset in the management of Alzheimer's disease.

Disclosure of Interest: None declared.

PP265—ATTENUATION OF ALUMINIUM INDUCED NEURODEGENERATION BY 4-METHYLESCULETIN

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Introduction: Aluminium is a potent neurotoxin and has been associated with Alzheimer's disease (AD). Prolonged aluminium exposure induces oxidative stress and contributes to the development of neurodegeneration. Current treatment modalities for AD provide only symptomatic relief, thus necessitating the development of new drugs with multiple targeting strategies. The aim of the study was to demonstrate the protective effect of chronic administration of 4-methylesculetin (4-ME) against aluminium-induced cognitive dysfunction and oxidative damage in rats.

Patients (or Materials) and Methods: Wistar rats (180–200 g) were divided into 6 groups (n = 6). Group I was the control group and group II received aluminium chloride (100 mg/kg PO) for a period of 42 days. Group III and IV received 4-ME (50 and 100 mg/kg PO) daily 1 hour before aluminium chloride (100 mg/kg PO) for 42 days while groups V and VI received only 4-ME (50 and 100 mg/kg PO) daily for 42 days. On the 21st and 42nd day, behavioral studies