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ORIGINAL INVESTIGATION

Extrapyramidal reactions following treatment with antidepressants: Results of the AMSP multinational drug surveillance programme

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ABSTRACT

Objectives: Extrapyramidal symptoms (EPS) are a common adverse effect of antipsychotics. However, there are case reports describing EPS following treatment with antidepressants. It is not fully understood how antidepressants cause EPS, but a serotonergic input to dopaminergic pathways is a probable mechanism of action.

Methods: Data from a multicenter drug-surveillance programme (AMSP, 'drug safety in psychiatry') which systemically documents severe drug reactions during psychiatric inpatient admissions, were reviewed to assess for EPS associated with antidepressant treatment. We identified 15 such cases, which were studied to detect similarities and to characterise risk factors.

Results: We report on 15 patients with EPS following antidepressant-therapy between 1994 and 2016. EPS frequently occurred with selective serotonin reuptake inhibitor (SSRI) treatment alone (7/15 cases) or concomitant SSRI treatment (6/15 cases). EPS were most frequent with escitalopram-treatment (5 cases). The most common EPS was atypical dyskinesia (6/15 cases) followed by akathisia (4/15 cases). The mean age of onset for EPS was 54.93 years (SD 17.9). EPS occurred at any dosage and equally often in men and women.

Conclusions: Our results highlight the possibility of EPS as an important, although uncommon, adverse effect of antidepressants. Clinicians should beware of this adverse effect and monitor early warning signs carefully.

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Antidepressants; extrapyramidal symptoms; EPS; AMSP; drug surveillance

Introduction

Extrapyramidal symptoms (EPS) are undesirable adverse effects that occur mainly in the context of antipsychotic treatment. As the name implies, these symptoms affect the extrapyramidal system, the part of the motor system responsible for involuntary or unconscious movement (Sachdev 2005).

EPS can present in a variety of ways, and five different syndromes have been described: akathisia, acute dystonia, malignant neuroleptic syndrome (MNS), parkinsonism and tardive dyskinesia (Fahn et al. 2011). Akathisia is the subjective perception of restlessness. It is extremely distressing for patients, who are often unable to sit still and describe the need for continuous movement. It usually occurs shortly after commencement or dose increase of antipsychotic medication. Tardive dyskinesia, conversely, is a condition which results from long-term (typically several years, at least several months) antipsychotic treatment. It is characterised by stereotypical, involuntary movements usually affecting the oropharyngeal region (tongue and throat) and facial muscles. The symptoms of acute dystonia involve a contraction of a muscle group to the maximal limit. Often, the sternocleidomastoid muscle (torticollis) and the tongue are involved, but the contractions can also be widespread (i.e., opisthotonus) (Semple and Smyth 2013). MNS is a potentially life-threatening complication of psychotropic medication usually involving antipsychotic drugs but also, less commonly, antidepressants (Lu et al. 2006; Tanii et al. 2006; Uguz and Sonmez 2013). When fully developed, symptoms include confusion, rigidity, hyperthermia, hyperhidrosis, tremor, autonomic dysregulation, and increased creatinine kinase (Fahn et al. 2011). Antipsychotic medications can also quite commonly cause parkinsonism, a clinical

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syndrome of bradykinesia, rigidity and tremor and postural instability.

EPS are thought to be caused by postsynaptic dopamine-2 (D2) receptor blockade in the substantia nigra of the basal ganglia and are therefore mainly attributed to antipsychotics. However, EPS following treatment with antidepressants have been described in case reports since 1958 (Hawthorne and Caley 2015). Clinicians may not be aware of the potential for drugs which lack postsynaptic D2 receptor blockade, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) to cause EPS. Thus, the symptoms may not be clinically recognised and, therefore, remain untreated.

Numerous case reports of EPS and even MNS during therapy with antidepressants have been reported (Madhusoodanan and Brenner 1997; Tanii et al. 2006; Jakob and Wolf 2007; Gaanderse et al. 2016), but data are lacking on the exact rate of antidepressant-related EPS. For example, in the study of Van Geffen et al. (2007), which used data of 258 patients treated with antidepressants from an internet-based medicine reporting system in the Netherlands, extrapyramidal effects following antidepressant treatment were amongst the 15 most frequently reported adverse effects by health care practitioners. However, the reporting physicians in this study had no consistent scoring system for EPS, and it is not clear whether there were inter-individual differences in EPS definition as well as detection amongst the physicians, thus leading to underestimation or wrong diagnosis of EPS. For example, there was no differentiation between inner tension, anxiety and akathisia in this study.

Acknowledging EPS as a possible adverse effect could prevent a patient from being treated wrongly, such as by an increase of antidepressant dosage due to misinterpreted behaviour (anxiety or agitated depression). Therefore, it is essential for practitioners to be aware of the probable association of EPS and antidepressants that are not routinely known for the cause of extrapyramidal effects.

The present case series aimed to analyse reports of EPS during antidepressant treatment in the drug surveillance database 'Arzneitmittelsicherheit in der Psychiatrie – drug safety in psychiatry' (AMSP). Furthermore, we analysed illness-related aspects, sociodemographic characteristics and probable risk factors for EPS.

Materials and methods

AMSP setting

AMSP is a multinational drug surveillance programme that collects data about severe adverse drug reactions (ADRs) during psychiatric inpatient admissions. It permits continuous pharmacovigilance of psychiatric inpatients from hospitals in Austria, Germany and Switzerland. Overall, 110 hospitals participated in the programme from 1993 to 2016.

Psychiatrists responsible for identifying ADRs (so-called 'drug monitors') liaise with and question their colleagues at frequent intervals to actively identify cases. They collect data using a standardised questionnaire and document cases with accompanying information on demographic characteristics, and psychiatric and medical history. Also, risk factors for the ADR along with possible alternative causes are explored. Finally, the drug monitors document and register actions taken as part of the management of the ADR. Cases are discussed at regional and central AMSP meetings, which are held twice a year. All drug monitors, as well as representatives of the national drug regulation authorities and drug safety experts of the pharmaceutical industry, are invited to join these regular meetings to discuss adverse effects and probable explanations. Each year, there are two 'reference days' held. On these two days which are set by AMSP, data on all administered drugs, age, sex and diagnosis of inpatients are collected and evaluated. The contributing hospitals from the three countries report their total number of inpatients and the mean duration of treatment for patients under drug surveillance.

Data concerning ADRs are recorded and stored in the central AMSP database for research purposes. Case reports are sent to the authorities and pharmaceutical companies. The detailed AMSP methodology has been described elsewhere (Grohmann et al. 2014). For this publication, the evaluated data was obtained from the anonymized AMSP database. The identity of individual patients can therefore not be traced.

Evaluations based on the AMSP database have been approved by the Ethics Committee of the University of Munich and the Ethics Committee of the Hannover Medical School (no. 8100_BO_S_2018). This study adheres to the Declaration of Helsinki and its later amendments. The AMSP programme is a continuous observational post-marketing drug surveillance programme and does not interfere with the ongoing clinical treatment of patients under surveillance.

In the AMSP database, every adverse reaction is classified according to a probability rating:

Grade 0: No relation

Grade 1: possible (ADR unknown or alternative explanation more likely)

Grade 2: probable (ADR is known for the drug in question and time course and dosage in accordance with previous experience; alternative explanation less probable)

Grade 3: definite (the same as G*rade 2* together with reappearance after re-exposure to the drug in question)

Grade 4: questionable or not sufficiently documented.

For extrapyramidal reactions, all cases with severe akathisia, tardive dyskinesia, acute dystonia, parkinsonism, atypical dyskinesia or more than one symptom were assessed. EPS were rated as 'severe' when they significantly impacted the course of treatment (thereby seriously endangering the patient's health) or when they were followed by significant functional impairment. Further, the AMSP protocol provides additional guidelines for the description of severe EPS (Grohmann et al. 2014): MNS and catatonic neuroleptic syndrome (a combination of akinesia, rigour, mutism and regressive behaviour (Caroff et al. 2002); tardive dyskinesia; acute dystonia and parkinsonism, if severely disabling in everyday functioning; akathisia (grade 4 or more according to the Barnes akathisia rating scale (Barnes 1989)); all cases of Pisa syndrome and atypical dyskinesias as unusual manifestations (Stübner et al. 2004).

The term 'atypical dyskinesia' was used to summarise several atypical EPS episodes including acute dystonia but with late onset, EPS similar to tardive dyskinesia but with early onset and other EPS with an uncommon clinical appearance (Stübner et al. 2004). EPS were diagnosed by experienced consultant psychiatrists and drug monitors.

In addition to reviewing the AMSP database, we performed a literature review on the topic. We searched for case reports in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) using the following keywords '*EPS*', '*extrapyramidal symptoms*', '*antidepressants*', '*SSRI*', '*case report*' and the names of various antidepressants.

Inclusion and exclusion criteria

For this analysis, all cases of severe EPS attributed solely to antidepressants (one or more antidepressants) were included and rated as possible, probable or definite ADR. All cases involving other drugs found to be responsible for causing EPS (for example first- and second-generation antipsychotics) were excluded from the analysis.

Polypharmacy

In psychiatric inpatients, combinations of pharmaceutical agents with known potential to cause EPS are commonly prescribed. In our data analysis and case description, only patients either treated with one antidepressant alone or combination therapy of two or more antidepressants were included. The term 'imputed alone' describes the following circumstance: there is a probable or definite causal relationship between ADR and one single substance.

Statistical analysis

Descriptive statistics (average and standard deviation) are used to describe sociodemographic and illness-related characteristics in this case series.

Results

Sociodemographic and illness-related data

From 1993 to 2015, a total of 15 cases of EPS following treatment with antidepressants have been reported to the AMSP programme (see Table 1). During this period, 243.588 inpatients treated with antidepressants were under surveillance. In total, 960 EPS cases were reported (13% of all severe ADRs), the vast majority of these being attributed to medications other than antidepressants. We focussed on the 15 cases in which EPS developed after treatment with antidepressants only.

A total of 8 patients developed EPS after antidepressant monotherapy while 7 cases were reported following treatment with a combination of two antidepressants. None of the patients received more than two antidepressants at the same time. The mean age of onset for EPS was 54.93 years (SD 17.9), and there was no gender difference noted (female: 8 cases; male: 7 cases).

Not surprisingly, most (9 of 15) of the patients who developed EPS after antidepressant treatment had a diagnosis from the category of affective disorders (F3 according to ICD-10 (Dilling et al. 1991)). The remainder had a variety of different diagnoses; three patients were documented as suffering from 'anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders' (F4), one patient had a diagnosis of 'schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders' (F2) and two patients were classified as having 'mental disorders due to known physiological conditions' (F0).

In terms of the sub-categories of the F3 group; three patients were diagnosed with recurrent severe major depressive disorder (MDD), without psychotic features (ICD-10 F33.2), two were diagnosed with recurrent moderate MDD (F33.1), one patient was diagnosed with recurrent severe MDD with psychotic symptoms (F33.2), one patient was diagnosed with a single moderate episode of MDD (F32.1) and one

Table 1. Antidepressants and sociodemographic characteristics of patients with extrapyramidal symptoms (EPS) reported to the AMSP programme.

EPS type	Antidepressant (probability rating)	Dosage at onset of EPS (mg)	Time to onset of EPS (days)	Age (<65 years = 1; >65 years = 2)	Sex (female = 1, male = 2)	Pre-existing risk factors	Remarks
Akathisia	Citalopram (2)	30	15	1	1	None	The patient had a co-medication with olanzapine which was slowly titrated after a manic episode from 20 to 2.5 mg. The patient did not have EPS with olanzapine. At the time of onset of EPS, the olanzapine dosage was at 2.5 mg.
Akathisia	Sertraline (2), Mirtazapine (0)	100 15	18	1	1	Rapid dose increase before onset of EPS	Mirtazapine was given the probability of 0 because, after discontinuation of sertraline, the dosage of mirtazapine was increased to 22.5 mg without any notable side effects.
Akathisia	Mirtazapine (3), Escitalopram (1)	90 40	36	2	2	None	Mirtazapine was given the probability of 3 because the patient developed akathisia after re-exposureto 90 mg; the probability of 1 was given to escitalopram because akathisia ceased after dose reduction of mirtazapine.
Akathisia	Citalopram (1), Trimipramine (0)	40 25	17	1	2	Pre-existing cerebrovascular haemorrhage	Trimipramine was given the probability rating of 0 because akathisia ceased during a dosage increase to 125 mg.
Atypical dyskinesia	Citalopram (1)	20	80	2	2	Parkinson's disease (medication-independent)	
Atypical dyskinesia	Sertraline (1)	100	10	1	1	Discrete brain atrophy, sensitivity to side effects of psychotropic medication, rapid dose increase before onset of EPS	
Atypical dyskinesia	Sertraline (1)	150	384	1	2	None	
Atypical dyskinesia	Fluoxetine (1)	40	27	1	2	None	
Atypical dyskinesia	Venlafaxine (2), Nortriptyline (1)	37.5 50	2	2	1	Migraine, multifactorial gait disorder	
Atypical dyskinesia	Trimipramine (2), Escitalopram (2)	75 5	4	1	2	Rapid dose increase before onset	
Early dyskinesia	Mirtazapine (1)	30	1	2	1	Alzheimer's disease	
Early dyskinesia	Escitalopram (2)	10	9	1	1	None	
Parkinsonism	Escitalopram (2)	10	8	2	1	Vascular encephalopathy	
Parkinsonism	Escitalopram (2), Mirtazapine (0)	20	10	2	1	Disturbances in cerebral perfusion	Mirtazapine was given the probability rating of 0 because it was started 2 months before onset of parkinsonism and its dosage was not changed.
Parkinsonism	Sertraline (2), Mirtazapine (1)	100 15–30	19	1	2	Rapid dose increase before onset	

Reports are from the years 1994 to 2016.

patient with a single episode of MDD, severe without psychotic features (F32.2). Furthermore, one patient was diagnosed with bipolar disorder, with a current severe depressive episode with psychotic features (F31.5).

46.67% ($n = 7$) of patients had concomitant neurological disorders such as a history of Parkinson's disease ($n = 1$), spastic hemiparesis after a haemorrhage of the basal ganglia ($n = 1$), discrete brain atrophy ($n = 1$), a history of a transient ischaemic attack in the territory of the middle cerebral artery and small post-ischaemic structure defects of the cerebellum ($n = 1$), Alzheimer's disease ($n = 1$), vascular encephalopathy ($n = 1$) and migraine ($n = 1$).

EPS types

Concerning EPS type, most of the patients ($n = 6$) suffered from atypical dyskinesia following antidepressant treatment, four patients suffered from akathisia, three from acute dystonia and two from parkinsonism. More specifically, atypical dyskinesia (Stübner et al. 2004) presented with: (1) intermittent conditions of neck hyperextensions lasting for 30 min following a 9 days treatment with 100 mg of sertraline, (2) spasms of jaw muscles with a 19 days latency period after increase of dosage of sertraline, (3) bruxism and spasms of the jaw and the tongue after one month of treatment with fluoxetine, (4) progredient hyperkinesia of the face and the extremities after add-on therapy of 37.5 mg of venlafaxine to a 19 years prior started therapy with nortriptyline, (5) intermittent hypokinesia and dystonia of facial musculature and extremities after 2.5 month treatment with citalopram, (6) uncontrollable twitching of facial musculature, shoulders, neck and right arm after add-on therapy of escitalopram to trimipramine and dose increase of trimipramine.

Drugs involved in EPS

In 13 of 15 EPS cases, SSRIs have been involved, in 7 cases EPS occurred with SSRI treatment alone. Tricyclic antidepressants (TCA) were only involved in combination therapies (one case with venlafaxine and nortriptyline and two cases with trimipramine and escitalopram).

EPS were observed in five patients treated with escitalopram (two cases with escitalopram alone; three in combination with either mirtazapine or trimipramine). Four cases occurred in connection with sertraline (two in combination with mirtazapine), two cases with citalopram alone, one case with mirtazapine alone and three cases in combination with mirtazapine (two in combination with escitalopram and one in combination with sertraline), one case with fluoxetine alone and one case with a combination therapy of venlafaxine and nortriptyline. We noted several patterns: EPS occurred mostly with SSRI treatment alone (7 out of 15 cases) or concomitant SSRI treatment (6 out of 10 cases) without a relation to the average dosage of drugs. Only four patients had a rapid increase in the prescribed dosage before the occurrence of EPS symptoms. The other patients had a stable dosage over time.

Six cases were rated as grade 1 (possible), 8 as grade 2 (probable) and one as grade 3 (definite) according to the AMSP classification described above.

The median time to onset of EPS following the commencement of psychotropic medication was 15 days. The mean time for onset of EPS was 42.67 ± 96.41 days. The time to onset of EPS was highly variable and ranged from 1 day (following treatment with mirtazapine) to 384 days (following treatment with sertraline). In this case, the treatment with sertraline had been commenced in an outpatient setting. The patient was admitted due to the adverse effect.

Seven patients developed EPS during combination therapy. In one specific case, remarkably severe parkinsonism occurred with combination therapy of sertraline and mirtazapine. The 45-year old patient showed a significant rigidity of the extremities and a bilateral cogwheel-phenomenon which interfered with his daily activities: he could not dress alone anymore, was unable to participate in the classes of occupational therapy and physiotherapy. This severe parkinsonism ceased after discontinuation of both sertraline and mirtazapine.

The patients who developed EPS following combination therapy were not significantly older than patients who developed EPS during antidepressant monotherapy ($t(14) = -0.37$, $P = 0.788$).

In 11 patients (five female and six male), the drug that might have caused EPS was discontinued. In nine cases a pharmacological intervention was necessary (e.g., biperiden). In two cases a reduction of the dose was tried before discontinuing the antidepressant, in a further two cases the dose was reduced, which led to an improvement of symptoms.

In four cases there could have been an alternative explanation for the EPS: one case with severe akathisia, which could have also been due to agitated depression, one case with atypical dyskinesia (intermittent conditions of neck hyperextensions lasting for 30 min), which could have been atypical non-epileptic seizures, one

case with atypical dyskinesia (intermittent dysarthria, contractions of the tongue and bruxism in the course of fluoxetine treatment), which could have been due to benzodiazepine withdrawal, and a drug-independent onset of Parkinson's disease.

Table 1 gives detailed information about the antidepressants and the characteristics of patients with EPS reported to the AMSP programme between 1994 and 2016.

Discussion

Fifteen patients with EPS following antidepressant treatment have been identified within the AMSP drug surveillance programme.

In 13 of 15 EPS cases, SSRIs were involved, and EPS occurred with SSRI treatment alone in seven cases. Five patients were treated with the SSRI escitalopram at onset of EPS, while four were treated with sertraline, the two most commonly used SSRIs in this time period.

Among the class of antidepressants, SSRIs are considered relatively safe and are therefore widely used for a variety of clinical conditions. However, reviews have pointed out that SSRIs belong to the class of antidepressants that are rather frequently reported to induce movement disorders (Madhusoodanan et al. 2010; Hawthorne and Caley 2015). Escitalopram, the enantiomer of citalopram, is a widely used SSRI that is commonly prescribed for patients with depression, anxiety, panic disorder or obsessive-compulsive disorder. With regard to neurological symptoms, headache, nausea, and tremor are considered to be the most common neurological adverse effects caused by escitalopram. Generally, EPS are considered as a rare adverse effect of escitalopram (Suresh and Gopalakrishnan 2018), whereas a review by the Food and Drug Administration found that the incidence of EPS in connection to escitalopram is as high as 12% (Madhusoodanan et al. 2010).

Sertraline is widely used in major psychiatric disorders, especially in depression. EPS following sertraline treatment are infrequent. However, severe EPS in connection to sertraline were recently described in adolescents (Wang et al. 2016). According to the data by the Food and Drug Administration, approximately 10% of all SSRIs associated EPS are caused by sertraline in adults (Madhusoodanan et al. 2010).

In a nested case–control study by Guo et al. (2018) with 3,838 subjects, escitalopram showed a risk ratio of 3.23 (95% CI, 2.44–4.26) for the development of EPS. In this study, EPS were most common when SNRIs were used. Duloxetine displayed the highest risk (5.68; 95% CI, 4.29–7.53). In contrast, we detected just one case of EPS involving the SNRI venlafaxine in combination with nortriptyline.

Interestingly, the most common reported EPS in our case series was atypical dyskinesia (6/15 cases), which is an AMSP term summarising cases with atypical EPS episodes including acute dystonia but with late onset, EPS similar to tardive dyskinesia but with early onset, and other EPS with an uncommon clinical appearance (Stübner et al. 2004).

The underlying cause of EPS following treatment with antidepressants is not clear yet. There are several possible pathophysiological pathways:

1. antidepressants cause a dopaminergic inhibition in the ventral tegmental area and the nigrostriatal tract (Gill et al. 1997; Madhusoodanan et al. 2010);
2. SSRIs cause a motor disturbance by altering postsynaptic dopamine receptors in the basal ganglia (Lane 1998);
3. tyrosine-hydroxylase, the speed limiting enzyme in dopamine synthesis, is decreased by SSRIs in the substantia nigra (MacGillivray et al. 2011);
4. serotonin transporter inhibition activates microglia and inhibits tyrosine hydroxylase causing low levels of dopamine (MacGillivray et al. 2011);
5. high serotonin levels caused by SSRIs hyperpolarize neuroendocrine tuberoinfundibular dopamine neurons (further, SSRIs such as sertraline directly suppress tuberoinfundibular neuron activity independent of serotonin neurotransmission) (Lyons et al. 2016);
6. changes of the gut microbiota following treatment with antidepressants (Cussotto et al. 2019) may influence D2 receptor expression corresponding to the inhibitory, indirect pathway of the striatum (Jadhav et al. 2018).

Because the mesolimbic dopaminergic system is responsible for the response to positive feedback, motivation and joy (Förstl et al. 2006; Argyropoulos and Nutt 2013), this suggests that a lack of dopamine in the ventral striatum is responsible for anhedonia, a key feature of depression. Therefore, current therapy approaches of treatment-resistant depression also include dopamine agonists such as pramipexol (Barone et al. 2010; Inoue et al. 2010) and norepinephrine-dopamine reuptake inhibitors, such as bupropion (Cheon et al. 2017).

According to the reviews by Madhusoodanan et al. (2010) and Hedenmalm et al. (2006), the potential risk

factors for EPS during antidepressant treatment are advanced age, female gender, pre-existing extrapyramidal disorders, concomitant antipsychotic medication and genetic alterations (CYP2D6 phenotype, serotonin, and dopamine transporter and receptor polymorphisms). Our data partly reflect these risk factors: the average age of our patients was 54.93 years; however, with a high standard deviation of 17.9 years. There was no difference regarding age in the group treated with one antidepressant or a combination of antidepressants. EPS were equally often reported in men and women (8 females; 7 males).

Other predisposing factors that must be considered are pre-existing medical conditions, especially neurological conditions involving the basal ganglia. Seven out of 15 patients had concomitant neurological disorders. Two had pre-existing alterations of the basal ganglia (Parkinson's disease and spastic hemiparesis after bleeding of the basal ganglia), which may have predisposed them to develop EPS. Other neurological disorders involved were Alzheimer's disease and migraine. Interestingly, atrophic changes of the basal ganglia are also reported in these disorders (Yuan et al. 2013; Cho et al. 2014). In the case of Parkinson's disease, motor signs do not appear until approximately 80% of the dopamine in the striatum or putamen is lost (Bernheimer et al. 1973). When EPS follow the use of antidepressants, the clinician should, therefore, consider their antidopaminergic effect and examine the patient thoroughly for any indication of an underlying basal ganglia disorder.

We included patients who received antidepressants only. There are indications in the literature that SSRIs may contribute to a higher risk of EPS with other concurrent medications, such as antipsychotics (Madhusoodanan et al. 2010) or polypharmacy (Hirano 2018). However, these interactions were not within the scope of this paper.

As already described in the report by Madhusoodanan et al. (2010), there seems to be no relationship between the dosage of the antidepressant agent and the occurrence of EPS. In addition, there appears to be no relationship between EPS and the duration of treatment.

Conclusion

Although EPS after antidepressant treatment are rare, clinicians should be alert and know about the possibility of this severe ADR caused by antidepressants. More research is needed to identify long- and short-term extrapyramidal side effects of antidepressants and their influence on the dopaminergic system. EPS could be an early warning sign of basal ganglia affections. Therefore, clinicians should monitor their patients carefully during antidepressant therapy.

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Statement of interest

Renate Grohmann and Sermin Toto are involved in the project management of AMSP. Sermin Toto has been a member of an advisory board for Otsouka and has received speaker's honoraria from Janssen Cilag, Lundbeck, Otsouka and Servier. Sabrina Mörkl has received speaker's honoraria from Allergosan. Siegfried Kasper received grants/research support, consulting fees and/or honoraria within the last three years from Angelini, AOP Orphan Pharmaceuticals AG, Celgene GmbH, Eli Lilly, Janssen-Cilag Pharma GmbH, KRKA-Pharma, Lundbeck A/S, Mundipharma, Neuraxpharm, Pfizer, Sage, Sanofi, Schwabe, Servier, Shire, Sumitomo Dainippon Pharma Co. Ltd. and Takeda. All authors declare that they have no conflict of interest which could have influenced the outcome of this publication.

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Austrian companies: AstraZeneca Österreich GmbH, Boehringer Ingelheim Austria, Bristol–Myers Squibb GmbH, CSC Pharmaceuticals GmbH, Eli Lilly GmbH, Germania Pharma GmbH, GlaxoSmithKline Pharma GmbH, Janssen-Cilag Pharma GmbH, Lundbeck GmbH, Novartis Pharma GmbH, Pfizer Med Inform, Servier Pharma Austria, Wyeth Lederle Pharma GmbH.

German companies: Abbott GmbH & Co. KG, AstraZeneca GmbH, Aventis Pharma Deutschland GmbH GE-O/R/N, Bayer Vital GmbH & Co. KG, Boehringer Mannheim GmbH, Bristol-Myers-Squibb, Ciba Geigy GmbH, Desitin Arzneimittel GmbH, Duphar Pharma GmbH & Co. KG, Eisai GmbH, esparma GmbH Arzneimittel, GlaxoSmithKline Pharma GmbH & Co. KG, Hoffmann-La Roche AG Medical Affairs, Janssen-Cilag GmbH, Janssen Research Foundation, Knoll Deutschland GmbH, Lilly Deutschland GmbH Niederlassung Bad Homburg, Lundbeck GmbH & Co. KG, Nordmark Arzneimittel GmbH, Novartis Pharma GmbH, Organon GmbH, Otsuka-Pharma Frankfurt, Pfizer GmbH, Pharmacia & Upjohn GmbH, Promonta Lundbeck Arzneimittel, Rhone-Poulenc Rohrer, Sanofi-Synthelabo GmbH, Sanofi-Aventis Deutschland, Schering AG, Servier Pharma, SmithKlineBeecham Pharma GmbH, Solvay Arzneimittel GmbH, Synthelabo Arzneimittel GmbH, Dr Wilmar Schwabe GmbH & Co., Thiemann Arzneimittel GmbH, Trommsdorff GmbH & Co. KG

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