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Trimetazidine use in Parkinson's disease: Is it a resolved problem?

(Research Paper)

Dávid Pintér, MD, PhD[1]; Dániel Bereczki, MD, DSc[2,3]; András Ajtay, MD[2,3]; Ferenc Oberfrank, MD[4]; József Janszky, MD, DSc[1,5]; Norbert Kovács, MD, DSc[1,5]

[1]Department of Neurology, Medical School, University of Pécs, Pécs, Hungary
[2]Department of Neurology, Medical School, Semmelweis University, Budapest, Hungary
[3]MTA-SE Neuroepidemiology Research Group, Budapest, Hungary
[4]Institute of Experimental Medicine, Budapest, Hungary
[5]MTA-PTE Clinical Neuroscience MR Research Group, Pécs, Hungary

Correspondence to:
Dr. Dávid Pintér
Department of Neurology
University of Pécs
7623, Pécs, Rét utca 2
Hungary
Telephone: +36 72 535 900
Fax: +36 72 535-911
e-mail: david_pinter@outlook.com

ORCID IDs:

Dávid Pintér: 0000-0002-0734-6878

Dániel Bereczki: 0000-0002-8374-0500

András Ajtay: 0000-0003-0194-2596

Ferenc Oberfrank: 0000-0002-2221-1314

József Janszky: 0000-0001-6100-832X

Norbert Kovács: 0000-0002-7332-9240

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ABSTRACT

Trimetazidine, an antianginal drug, can worsen the symptoms of movement disorders, therefore, the European Medicines Agency (EMA) recommended avoiding the use of this drug in Parkinson's disease (PD). We investigated the impact of this recommendation on the observed trend of trimetazidine use in PD in Hungary from 2010 to 2016 by conducting a nationwide, retrospective study of health administrative data of human subjects. Interrupted time series analyses were performed to explore changes in user trends after the EMA recommendations. We found that trimetazidine use in PD decreased by 6.56% in each 6-month interval after the EMA intervention (a change in trend of -530.22, 95% CI = -645.00 to -415.44, $p < 0.001$ and a decrease in level of -567.26, 95% CI = -910.99 to -223.53, $p = 0.005$ 12 months postintervention). Trimetazidine discontinuation was the highest immediately after the intervention, however, its rate slowed down subsequently (a change in trend of -49.69, 95% CI = -85.14 to -14.24, $p = 0.11$ without significant level effects). The rate of new trimetazidine prescriptions did not reduce significantly, therefore, the decreased overall use was mainly attributable to the increased rate of discontinuation only. The main indications for trimetazidine use were circulatory system disorders, especially angina pectoris, however, off-label utilization was also considerable (40%). The EMA recommendations on trimetazidine use seem to be only moderately effective in Hungary. Although the number of patients with PD on the drug modestly decreased after the EMA restrictions, trimetazidine is still widely used in PD for both on- and off-label indications.

SIGNIFICANCE STATEMENT

Trimetazidine can worsen the symptoms of movement disorders in a clinically relevant manner and its use is consequently not recommended in Parkinson's disease (PD) by the European Medicines Agency (EMA). The impact of the EMA recommendations on trimetazidine use in PD has not yet been evaluated, therefore, we conducted a nationwide, retrospective study to address this question in Hungary. According to our results, the restrictions on trimetazidine use are only moderately effective. Although the number of patients with PD on the drug modestly decreased after the EMA recommendations, trimetazidine is still widely used in PD for both on- and off-label indications. Our findings promote another safety communication to resolve a clinically important problem and to improve the management of patients with PD.

INTRODUCTION

Trimetazidine (TMZ), a widely used antiischemic drug in Europe, is usually prescribed as a long-term treatment for angina pectoris (cardiological indication), and in some countries for tinnitus, vertigo/dizziness (otological indications) and visual disturbances (ophthalmological indications). Because medicines containing TMZ had been reported both causing reversible parkinsonism, tremor, and orofacial dyskinesia (Marti Masso et al., 2004; Marti Masso et al., 2005; Masmoudi et al., 2005; Sommet et al., 2005; Sivet et al., 2008), and worsening the symptoms of existing movement disorders such as Parkinson's disease (PD) (Marti Masso et al., 2005), the French National Pharmacovigilance Commission recommended the reevaluation of the role of TMZ in antianginal treatment on 19 May 2009 (Commission nationale de pharmacovigilance, 2009). The results of this safety analysis led to the suspension of the French authorization of TMZ on 7 April 2011 (Réunion de la Commission d'AMM, 2011). Due to the concerns of the French medicines regulatory agency over the safety and efficacy of TMZ, the European Medicines Agency (EMA) also reviewed the benefits and risks of the drug between 22 April 2011 and 22 June 2012 (European Medicines Agency, 2012). After the review, the drug was delicensed as a treatment option for tinnitus, vertigo, and vision disturbances, and prescription of TMZ became contraindicated in patients having PD or severely reduced kidney function (European Medicines Agency, 2012). Furthermore, TMZ has only been recommended as a second-line treatment for angina pectoris in accordance with the EMA restrictions and recent guidelines for the management of chronic coronary syndromes (European Medicines Agency, 2012; Knuuti et al., 2020).

Although other antianginal medications with similar level of evidence are also available as second-line treatments (Danchin et al., 2011; Knuuti et al., 2020), TMZ has remained to be one of the most frequently used agents in the symptomatic treatment for angina pectoris (Ponikowski et al., 2016; Pinter et al., 2019). Furthermore, its use in patients with PD also seems to remain extensive (Kwon et al., 2019; Pinter et al., 2019) despite published warnings concerning TMZ treatment and the clear recommendation against the prescription of TMZ in movement disorders.

Postmarketing safety analyses of available drugs have an essential role in reaching and maintaining high-quality patient care. In the European Union, both national pharmacological agencies and the EMA have their pharmacovigilance services to monitor drug safety. Recently, numerous safety warnings have been

made by international regulatory agencies for various neurological agents. Similarly to TMZ in PD, the EMA took regulatory actions for valproic acid (VPA) use in girls, women of childbearing age, and pregnant females based on postmarketing data. Although the efficacy of the restrictions on VPA use by the EMA has been thoroughly evaluated (European Medicines Agency, 2014; Vajda et al., 2014; Wen et al., 2015; Liu et al., 2017; Karlsson et al., 2018; Kinney et al., 2018; Virta et al., 2018; Jacob et al., 2019; Puteikis et al., 2019), only little efforts have been made to generate such information concerning the impact of the EMA warning on the clinical practice with TMZ thus far (von Bredow et al., 2018). Therefore, we conducted a study in Hungary, a country in the European Union with a population of about 10 million of which approximately 400,000 inhabitants suffered from stable coronary heart disease in 2018 (Pinter et al., 2019). Our aims were as follows:

1.) To determine, whether there is any change in the trend of TMZ use among patients with PD after the EMA recommendations;
2.) To compare trends of TMZ discontinuation in PD before and after the EMA restrictions;
3.) To compare trends of new TMZ prescriptions among PD patients before and after the EMA regulatory intervention;
4.) To explore the indications for ongoing TMZ treatment and new prescriptions in the PD population.

METHODS

Study design

A nationwide, retrospective study of anonymized healthcare administrative data of both male and female human subjects was conducted to assess the effectiveness of the EMA regulatory event on TMZ use. The data evaluated in this study was obtained from the database of the National Health Insurance Fund of Hungary, a country with a single-payer health insurance system. In this database, data on drug utilization regardless of being prescribed by state-funded or private services has been recorded since 2000 (Gresz, 2012). In respect of drug prescription refills, not only the social security numbers of patients but also data on the type and the dose of medications and the indications for prescriptions, that are indicated by the International Classification of WHO Diseases, 10th Revision, Clinical Modification (ICD-10-CM)

codes, are strictly recorded on an individual level. In addition, the database includes relevant data on both out- and inpatient care, therefore, it is suitable for detecting chronic medication use. Because both the reimbursement for medications and the funding of hospital care are performed based on these reports, this database is a reliable representation of data of patients in the Hungarian healthcare. Original patient identifiers were anonymized, and the encrypted patient identifier was used for linking medical information to prescription refills.

The study design was similar to that used by Puteikis et al. to assess the impact of the EMA regulation on VPA use (Puteikis et al., 2019). To evaluate changes in the numbers of PD patients treated with TMZ, new prescriptions on TMZ and withdrawal of the drug in PD over time, the analysis of an interrupted time series model was applied. This method has previously been described in more detail elsewhere (Ramsay et al., 2003; Bernal et al., 2017).

Study data

In the first analysis aiming to evaluate the change in overall TMZ use in PD, patient reimbursement information for TMZ [Anatomical Therapeutic Chemical (ATC) code C01EB15] was used from 2010 to 2016. A total of 464,116 subjects treated with TMZ in this period were identified. Only patients aged older than 18 years at the initiation of TMZ, having the diagnosis of PD (ICD-10-CM code G20), treated with antiparkinsonian medications (ATC code N04) - as a confirmation of the diagnosis of PD-, and with concomitant TMZ use were finally included in this analysis. We analyzed data for every half-year because according to the EMA recommendation, there had been no need for urgent intervention, changes in treatment introduced at the "next routine appointment" had been acceptable (European Medicines Agency, 2012). To eliminate the effect of death on our results, data of patients who had died in the half-year examined was excluded. The outcome was the number of patients in the different half-years, and the date of the end of the EMA assessment procedure (22 June 2012) was the selected intervention point.

In another analysis, we examined the frequency of new TMZ prescriptions and TMZ discontinuation in PD between 2010 and 2016. To include data of a patient, the following criteria must have been met: (1) age older than 18 years at the initiation of TMZ; (2) the diagnosis of PD (ICD-10-CM code G20); and (3) treatment with antiparkinsonian medications (ATC code N04). During the extraction

of data of newly initiated patients, the diagnosis of PD must have been established prior to the first prescription of TMZ. With respect to TMZ discontinuation, efforts were made to eliminate the effects of death and intolerance to or ineffectiveness of TMZ on the results. Because patients are generally supplied with TMZ for 30 days with a prescription in Hungary, subjects with at least two consecutive prescriptions and consequently at least 60 days of treatment were considered as chronic TMZ users. Data for every half-year was evaluated in this subanalysis, and the date of the appearance of the EMA recommendations (22 June 2012) was used as an intervention point.

Finally, we attempted to identify the main indications for TMZ initiation and ongoing treatment in PD. Based on certain preselected ICD-10-CM codes, that were collected for each included subject, we made the following categorizations:

1. Antianginal indication (ICD-10-CM code I20, on-label prescriptions);
2. All other cardiological indications (ICD-10-CM codes I00-I99 with the exemption of I20, possibly off-label indications);
3. Opthalmological indications (ICD-10-CM H30-H36, definitely off-label indications after the EMA warning);
4. Otological indications (ICD-10-CM codes H80-H83, definitely off-label indications after the EMA warning).

This study protocol was approved by the 7603-PTE.2018 Institutional and Regional Ethical Board. All study-related procedures were performed in accordance with the Helsinki Declaration of 1975.

Statistical analysis

A non-seasonal autoregressive integrated moving average (ARIMA) model was used. All analyses were performed following the guidance provided by the Cochrane Effective Practice and Organization of Care Group (Cochrane Effective Practice and Organisation of Care, 2017).

The IBM SPSS software package (version 24.0.2, IBM Inc., Armonk, NY, USA) was used for all statistical analyses. The level of statistical significance was set at 0.05.

RESULTS

The absolute number of PD patients treated with TMZ showed a gradual increase of an average of 260 in each 6-month interval [95% CI = 172.38 to 346.80, $p < 0.001$] prior to the EMA assessment procedure which means an average increase of 5.64% in each half-year. The overall TMZ use in PD reached its maximum (5 098 patients) immediately after the intervention (the second half year of 2012). Subsequently, the number of PD patients treated with the drug showed an average decrease of 6.56% (269 patients) in each 6-month interval. According to the ARIMA model, there was a significant change in the preintervention trend of overall TMZ use in PD (-530.22, 95% CI = -645.00 to -415.44, $p < 0.001$). Additionally, we found a significant decrease in level delayed by 12 months (-567.26, 95% CI = -910.99 to -223.53, $p = 0.005$) and this effect remained significant during all subsequent postintervention 6-month periods examined by this study. The relative 54-month effect was -57.93% (Fig. 1A, Table 1).

TMZ discontinuation increased by 50.50% (40 patients) on average in each 6-month preintervention period. Withdrawal of the drug was the highest (347 patients) in the second 6-month period after posting the EMA recommendations (first half year of 2013). In the postintervention period, the average increase in TMZ discontinuation was only 3.51% (11 patients) in each 6-month interval. The ARIMA model globally detected a negative change in the preintervention trend of TMZ withdrawal (-49.69, 95% CI = -85.14 to -14.24, $p = 0.11$) without significant level effects. The relative 54-month effect was -62.69% (Fig. 1B, Table 2).

Regarding new TMZ prescriptions in the PD population, the average absolute number of new prescriptions among PD patients decreased by 119 in each 6-month interval (95% CI = -190.79 to -47.19, $p = 0.005$) prior to baseline (the first half year of 2012) which means an average decrease of 22.2% in each preintervention half-year period. There was a temporary increase of 47.7% in TMZ initiation immediately after the EMA intervention (the second half year of 2012) which was followed by a slight long-term decrease. Globally, the decrease in TMZ initiation slowed down and the average decrease in new prescriptions was only 6.54% (7 patients) per half-year after the EMA recommendations. Compared to baseline, no significant change in the absolute number of patients newly initiated on the drug was found on long-term after the EMA restrictions. The ARIMA model showed a negative change in the preintervention trend (105.42, 95% CI = 31.07 to 138.29, $p = 0.011$), combined with negative level

effects at 12 months postintervention (341.11, 95% CI = 9.48 to 672.74, p = 0.045) and at all following time points. The relative 54-month effect was -119.62% (Fig. 1B, Table 3).

Potential indications for TMZ utilization in PD are separately shown in regard to ongoing treatments and new prescriptions for every investigated year in Figure 2. The main underlying causes for ongoing TMZ use and initiation of the drug were circulatory system disorders, especially angina pectoris. However, of all detected diagnoses, the proportion of the only one on-label indication (angina pectoris) and other cardiological indications showed a slight continuous decrease over the years after the EMA recommendations for both ongoing treatment and drug initiation. In parallel, there was a modest shift towards definitely off-label TMZ prescription. In the last investigated year, definitely off-label indications might have still been responsible for 45% and 42% of all PD cases with ongoing TMZ treatment and TMZ initiation, respectively.

DISCUSSION

Although the EMA recommendations on TMZ use were introduced more than seven years ago, only a single study has attempted to investigate their impact on TMZ utilization thus far (von Bredow et al., 2018). Of note, this study provides no data on possible changes in the trend of TMZ use in PD. Therefore, we aimed to explore the effectiveness of the EMA restrictions specifically focusing on the management of patients suffering from PD.

The analysis of data obtained from the National Health Insurance Fund of Hungary using an interrupted time series model revealed that the EMA procedure seemed to lead to only moderate beneficial changes in TMZ utilization among patients with PD. The main result of introducing restrictions on TMZ use is the prevention of a further increase in the use of the drug in PD. However, only a slight difference was found between the absolute numbers of PD patients treated with medications containing TMZ at the beginning and the end of the period investigated in this study. In the first half year of 2010, there had been a total of 3950 patients with PD and concomitant TMZ use which number was reached again in the first half year of 2015 and subsequently decreased to 3090 by the second half year of 2016. This means a total of 21.8% decrease in overall TMZ use in PD over seven years. In the years analysed

by this study, there were approximately 20,000-40,000 patients having PD in Hungary (Gustavsson et al., 2011; Szatmari et al., 2019). Consequently, 7.7-15.5% of all PD patients in our country were TMZ users after the EMA restrictions. This data sheds light on that the number of PD patients on TMZ might be still large despite the recommendation against the prescription of this drug in the PD population.

Based on our findings, the effects of the EMA procedure on TMZ use in PD mainly resulted from the increased rate of withdrawal of the drug and not the reduction in the number of new TMZ prescriptions among PD subjects. Eventually, no significant reduction appeared in the frequency of new TMZ initiations in the PD population. In the study by von Bredow et al. investigating 12 European countries, including Hungary, between 2014 and 2015, less than half (46.5%) of the asked physicians mentioned PD as a contraindication for TMZ treatment (von Bredow et al., 2018). This gap in knowledge of a great part of physicians prescribing TMZ may explain our findings in regard to new PD patient initiations on the drug.

Although the majority of patients with PD received TMZ for angina pectoris, a relatively large portion of PD patients were treated with TMZ for possibly and definitely off-label indications. These included not just ophthalmologic and otologic but also some non-anginal cardiovascular disorders. These findings are in line with the results of the study by von Bredow et al. that also detected frequent off-label prescription of TMZ (von Bredow et al., 2018) after the EMA procedure. A possible explanation for the frequent off-label prescription of TMZ may be that the knowledge and awareness of physicians regarding the safety communications on TMZ and the updated indications of this drug are poor which may result from the ineffective risk minimization measures and the oversight, previous experience or old habits of physicians (von Bredow et al., 2018). Another reason of this finding may be that while recent guidelines on the treatment of angina pectoris provide many alternatives for TMZ (e.g., certain beta-blockers and calcium channel blockers, long-acting nitrates, and ranolazine) (Knuuti et al., 2020), pharmacotherapies for tinnitus, vertigo and visual disturbances of vascular origin are very limited (Brand, 2012; von Bredow et al., 2018; Cima et al., 2019). However, the use of TMZ in these disorders is also not favoured by clinical data (European Medicines Agency, 2012). Nonpharmacological treatments (e.g., neurostimulation, tinnitus retraining therapy, sound therapy, laser photocoagulation, photodynamic

therapy) (Brand, 2012; Cima et al., 2019) can be good alternatives if pharmacotherapy is ineffective or not recommended. Although our results show that TMZ use in PD regarding all indications seems to be still not negligible, the EMA intervention might have affected TMZ use among PD patients in every group of prescribers, first among cardiologists found to have the most up-to-date knowledge on recent regulations on TMZ utilization (von Bredow et al., 2018), and with some delay among ophthalmologists and otolaryngologists. However, it should be also noted that TMZ could have been withdrawn also by general practitioners or neurologists.

There is increasing research into potential new indications of TMZ (Tarkin and Kaski, 2018). Potential future approval of the drug as a treatment option for further disorders might detrimentally affect achieved improvements in TMZ utilization among patients with PD if prescribers are not aware of the harmful effects of TMZ on movement disorders. Considering the minimal clinically relevant difference thresholds for the Movement Disorders Society-sponsored Unified Parkinson's Disease Rating Scale (Horvath et al., 2015; Horvath et al., 2017; Makkos et al., 2019), medicines containing TMZ can worsen the symptoms of PD in a clinically relevant manner (worsening of 4.0, 3.5, 10.4, and 1.2 points in the Parts I, II, III, and IV of the Movement Disorders Society-sponsored Unified Parkinson's Disease Rating Scale), which can have a serious impact on the health-related quality of life (Pinter et al., 2020). These findings highlight the importance of compliance with the EMA recommendations in the management of PD patients having any comorbidities approved to be treated with TMZ at present and in the future.

The strength of the present study mainly lies in the used method that enabled the evaluation of changes in TMZ utilization trends among patients with PD with respect to the EMA intervention at a population level. However, for correct interpretation of the results, some potential limitations also need to be considered. First, we were able to obtain data on TMZ use only between 2010 and 2016 due to technical reasons, however, investigation of a wider period could provide a deeper knowledge of how trends in TMZ use have changed and possible underlying causes for these changes. As it can be seen in Figure 1B, TMZ initiation among PD patients started to decrease prior to the release of the EMA recommendations similarly to the increase in the withdrawal of the drug in PD. A possible explanation for this might be that literature data (Marti Masso 2004; Marti Masso et al., 2005; Masmoudi et al., 2005;

Sommet et al., 2005; Sivet et al., 2008; Commission nationale de pharmacovigilance, 2009; Réunion de la Commission d'AMM, 2011) prompting the EMA to reevaluate the role of TMZ might have already widely disseminated among physicians prior to the EMA recommendations. This might also be an alternative explanation for why the present study found the EMA restrictions to be only moderately effective. However, future trials that analyze data on TMZ prescription also from the years of the release of publications (Marti Masso et al., 2004; Marti Masso et al., 2005; Masmoudi et al., 2005; Sommet et al., 2005; Sivet et al., 2008) and events (Commission nationale de pharmacovigilance, 2009; Réunion de la Commission d'AMM, 2011) leading to the EMA procedure should evaluate this hypothesis. In addition, further studies providing data on the previous three years would also be helpful in obtaining a more reliable picture of the current practice with TMZ. Another issue may be that indication-linked reimbursement has not been available in regard to off-label prescription of TMZ in Hungary since the introduction of the EMA recommendations. This regulation might have had an impact on the practice of drug prescription, however, it should have not meaningfully affected the compliance with the EMA recommendations. Furthermore, the present paper did not analyze the correlation between TMZ use in PD and hospitalization or death. However, future investigations could provide additional useful data on the clinical relevance of the EMA recommendations by exploring whether TMZ treatment may lead to increased hospitalization rates and risk of death in PD. Finally, it should be also mentioned that only data representing TMZ use in Hungary was analyzed. Therefore, to judge the generalizability of our findings, further studies should be conducted in other countries where TMZ has been available. Our paper could be a good basis for planning and performing such investigations.

To conclude, the present study suggests that the EMA restrictions on TMZ use in PD are only moderately effective. The number of patients with PD on TMZ seems to remain relatively stable. Furthermore, off-label TMZ use in PD is still an unsolved problem. Possibly, another safety communication should be performed, perhaps via channels which have not previously been used (e.g., brochures, posters, advertisements on websites frequently visited by the prescribers of TMZ, mobile applications, seminars, and conferences) and with new strategies, for further education of physicians and gaining more compliance which might lead to an additional improvement in the management of PD

patients.

FOOTNOTES

The examination discussed in the paper is the own work of the authors with the help of government-based funds. We would like to thank Prof. Kálmán Tóth for his great help in making a better understanding of the importance of avoiding trimetazidine use in Parkinson's disease among the Hungarian cardiologists.

DECLARATIONS

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CONFLICT OF INTEREST

The authors declare no competing interests.

DATA AVAILABILTY

Because the Ethical Approval of the present study does not authorize the authors to publish the data, it is not made available.

AUTHOR ROLES

1. Research project:	A. Conception,	B. Organization,	C. Execution;
2. Statistical Analysis:	A. Design,	B. Execution,	C. Review and Critique;
3. Manuscript:	A. Writing of the first draft,	B. Review and Critique	

DP 1, 2, 3
DB 1B, 2C, 3B
AA 1B, 2C, 3B
FO 1A, 1B, 3B
JJ 1A, 2C, 3B
NK 1, 2, 3

FINANCIAL DISCLOSURES

DP reported no financial disclosure.
DB reported no financial disclosure.
AA reported no financial disclosure.
FO reported no financial disclosure.
JJ received <1000 EUR consultation fees from Hungarian subsidiaries of UCB, Richter, and Gerot. Regarding this study, the author did not receive any corporate funding.
NK received <1000 EUR consultation fees from Hungarian subsidiaries of Medtronic, Boehringer Ingelheim, Novartis, GlaxoSmithKline, UCB, Krka, and Abbvie. Regarding this study, the author did not receive any corporate funding.

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FIGURE LEGENDS

Figure 1. Patients having Parkinson's disease with ongoing trimetazidine treatment (A), new initiations or withdrawal (B) from 2010 to 2016 and interrupted time series models

Abbreviations: ***EMA*** *= European Medicines Agency;* ***PD*** *= Parkinson's disease;* ***TMZ*** *= trimetazidine*

Figure 2. Possible indications for ongoing trimetazidine treatment (A) and new initiations on the drug (B) in Parkinson's disease from 2010 to 2016*

*The following categorizations were used: 1.) Antianginal indication (ICD-10-CM I20, on-label prescriptions); 2.) Other cardiological indications (ICD-10-CM I00-I99 with the exemption of ICD-10-CM I20, possibly off-label prescriptions after the EMA warning); 3.) Ophtalmological indications (ICD-10-CM H30-H36, definitely off-label prescriptions after the EMA warning); and 4.) Otological indications (ICD-10-CM H80-H83, definitely off-label indications after the EMA warning). Other non-investigated disorders might have also served as the basis of trimetazidine use or initiation. One patient might have had more than one diagnosis.

Abbreviations: ***ICD-10-CM*** *= International Classification of WHO Diseases, 10th Revision, Clinical Modification*

Table 1. ARIMA model parameters for Figure 1A

ARIMA Model Parameters 1				Estimate	Standard error	t value	p value
Outcomes	No Transformation	Constant		3726.399	145,993	25.525	< 0.001
		AR	Lag 1	0.609	,446	1.364	0.206
Time period	No Transformation	Numerator	Lag 0	259.585	38,550	6.734	< 0.001
Phase	No Transformation	Numerator	Lag 0	3144.925	305,505	10.294	< 0.001
Interact	No Transformation	Numerator	Lag 0	-530.221	50,743	-10.449	< 0.001
ARIMA Model Parameters 2							
Outcomes	No Transformation	Constant		3725.494	145.369	25.628	< 0.001
		AR	Lag 1	0.605	0.447	1.352	0.209
Phase	No Transformation	Numerator	Lag 0	-37.185	133.227	-0.279	0.786
6 months preintervention	No Transformation	Numerator	Lag 0	259.901	38.473	6.755	< 0.001
6 months postintervention	No Transformation	Numerator	Lag 0	-270.593	29.031	-9.321	< 0.001
ARIMA Model Parameters 3							
Outcomes	No Transformation	Constant		3725.852	145.951	25.528	< 0.001
		AR	Lag 1	0.609	0.446	1.364	0.206
Phase	No Transformation	Numerator	Lag 0	-567.264	151.953	-3.733	0.005
12 months preintervention	No Transformation	Numerator	Lag 0	259.802	38.542	6.741	< 0.001
12 months postintervention	No Transformation	Numerator	Lag 0	-270.729	29.187	-9.276	< 0.001
ARIMA Model Parameters 4							
Outcomes	No Transformation	Constant		3725.668	145.560	25.595	< 0.001
		AR	Lag 1	0.606	0.447	1.356	0.208
Phase	No Transformation	Numerator	Lag 0	-1097.990	183.443	-5.985	< 0.001
18 months preintervention	No Transformation	Numerator	Lag 0	259.844	38.496	6.750	< 0.001
18 months postintervention	No Transformation	Numerator	Lag 0	-270.607	29.076	-9.307	< 0.001
ARIMA Model Parameters 5							
Outcomes	No Transformation	Constant		3724.868	145.799	25.548	< 0.001
		AR	Lag 1	0.608	0.447	1.362	0.206
Phase	No Transformation	Numerator	Lag 0	-1629.819	222.141	-7.337	< 0.001
24 months preintervention	No Transformation	Numerator	Lag 0	260.098	38.526	6.751	< 0.001
24 months postintervention	No Transformation	Numerator	Lag 0	-270.753	29.171	-9.282	< 0.001

ARIMA Model Parameters 6								
	Outcomes	No Transformation	Constant		3724.800	145.744	25.557	< 0.001
			AR	Lag 1	0.608	0.447	1.362	0.206
	Phase	No Transformation	Numerator	Lag 0	-2160.452	264.907	-8.156	< 0.001
	30 months preintervention	No Transformation	Numerator	Lag 0	260.093	38.520	6.752	< 0.001
	30 months postintervention	No Transformation	Numerator	Lag 0	-270.776	29.142	-9.291	< 0.001
ARIMA Model Parameters 7								
	Outcomes	No Transformation	Constant		3725.820	145.699	25.572	< 0.001
			AR	Lag 1	0.607	0.447	1.359	0.207
	Phase	No Transformation	Numerator	Lag 0	-2688.893	309.975	-8.675	< 0.001
	36 months preintervention	No Transformation	Numerator	Lag 0	259.782	38.514	6.745	< 0.001
	36 months postintervention	No Transformation	Numerator	Lag 0	-270.635	29.101	-9.300	< 0.001
ARIMA Model Parameters 8								
	Outcomes	No Transformation	Constant		3725.288	145.465	25.609	< 0.001
			AR	Lag 1	0.606	0.447	1.354	0.209
	Phase	No Transformation	Numerator	Lag 0	-3220.464	356.342	-9.038	< 0.001
	42 months preintervention	No Transformation	Numerator	Lag 0	259.944	38.486	6.754	< 0.001
	42 months postintervention	No Transformation	Numerator	Lag 0	-270.626	29.045	-9.317	< 0.001
ARIMA Model Parameters 9								
	Outcomes	No Transformation	Constant		3725.283	145.604	25.585	< 0.001
			AR	Lag 1	0.607	0.447	1.357	0.208
	Phase	No Transformation	Numerator	Lag 0	-3751.680	404.167	-9.282	< 0.001
	48 months preintervention	No Transformation	Numerator	Lag 0	259.969	38.501	6.752	< 0.001
	48 months postintervention	No Transformation	Numerator	Lag 0	-270.673	29.106	-9.300	< 0.001
ARIMA Model Parameters 10								
	Outcomes	No Transformation	Constant		3725.515	146.026	25.513	< 0.001
			AR	Lag 1	0.610	0.446	1.368	0.205
	Phase	No Transformation	Numerator	Lag 0	-4282.119	453.283	-9.447	< 0.001
	54 months preintervention	No Transformation	Numerator	Lag 0	259.869	38.551	6.741	< 0.001
	54 months postintervention	No Transformation	Numerator	Lag 0	-270.905	29.197	-9.279	< 0.001

Table 2. ARIMA model parameters for trimetazidine withdrawal in Figure 1B

ARIMA Model Parameters 1					Estimate	Standard error	t value	p value
Outcomes	No Transformation	Constant			82.121	47.138	1.742	0.115
		AR	Lag 1		-0.343	0.567	-0.605	0.560
Time period	No Transformation	Numerator	Lag 0		34.983	14.450	2.421	0.039
Phase	No Transformation	Numerator	Lag 0		327.730	75.612	4.334	0.002
Interact	No Transformation	Numerator	Lag 0		-49.690	15.668	-3.171	0.011
ARIMA Model Parameters 2								
Outcomes	No Transformation	Constant			82.142	47.147	1.742	0.115
		AR	Lag 1		-0.343	0.567	-0.605	0.560
Phase	No Transformation	Numerator	Lag 0		29.606	55.124	0.537	0.604
6 months preintervention	No Transformation	Numerator	Lag 0		34.977	14.453	2.420	0.039
6 months postintervention	No Transformation	Numerator	Lag 0		-14.705	6.041	-2.434	0.038
ARIMA Model Parameters 3								
Outcomes	No Transformation	Constant			82.141	47.146	1.742	0.115
		AR	Lag 1		-0.343	0.567	-0.605	0.560
Phase	No Transformation	Numerator	Lag 0		-20.078	65.658	-0.306	0.767
12 months preintervention	No Transformation	Numerator	Lag 0		34.977	14.452	2.420	0.039
12 months postintervention	No Transformation	Numerator	Lag 0		-14.706	6.041	-2.434	0.038
ARIMA Model Parameters 4								
Outcomes	No Transformation	Constant			82.139	47.146	1.742	0.115
		AR	Lag 1		-0.343	0.567	-0.605	0.560
Phase	No Transformation	Numerator	Lag 0		-69.764	77.938	-0.895	0.394
18 months preintervention	No Transformation	Numerator	Lag 0		34.978	14.452	2.420	0.039
18 months postintervention	No Transformation	Numerator	Lag 0		-14.706	6.041	-2.434	0.038
ARIMA Model Parameters 5								
Outcomes	No Transformation	Constant			82.137	47.145	1.742	0.115
		AR	Lag 1		-0.343	0.567	-0.605	0.560
Phase	No Transformation	Numerator	Lag 0		-119.451	91.262	-1.309	0.223
24 months preintervention	No Transformation	Numerator	Lag 0		34.979	14.452	2.420	0.039
24 months postintervention	No Transformation	Numerator	Lag 0		-14.706	6.041	-2.434	0.038

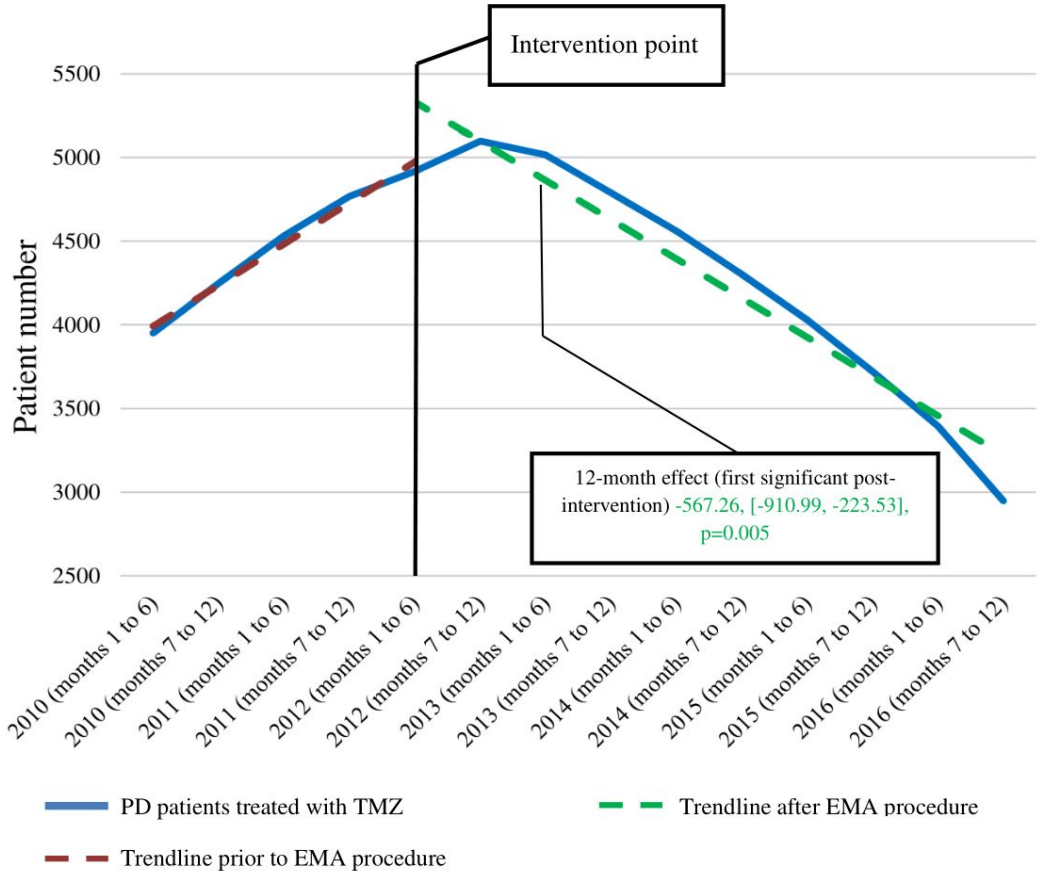
ARIMA Model Parameters 6								
	Outcomes	No Transformation	Constant		82.134	47.144	1.742	0.115
			AR	Lag 1	-0.343	0.567	-0.605	0.560
	Phase	No Transformation	Numerator	Lag 0	-169.141	105.233	-1.607	0.142
	30 months preintervention	No Transformation	Numerator	Lag 0	34.979	14.452	2.420	0.039
	30 months postintervention	No Transformation	Numerator	Lag 0	-14.706	6.041	-2.434	0.038
ARIMA Model Parameters 7								
	Outcomes	No Transformation	Constant		82.131	47.142	1.742	0.115
			AR	Lag 1	-0.343	0.567	-0.605	0.560
	Phase	No Transformation	Numerator	Lag 0	-218.834	119.624	-1.829	0.101
	36 months preintervention	No Transformation	Numerator	Lag 0	34.980	14.451	2.421	0.039
	36 months postintervention	No Transformation	Numerator	Lag 0	-14.706	6.041	-2.435	0.038
ARIMA Model Parameters 8								
	Outcomes	No Transformation	Constant		82.128	47.141	1.742	0.115
			AR	Lag 1	-0.343	0.567	-0.605	0.560
	Phase	No Transformation	Numerator	Lag 0	-268.529	134.300	-1.999	0.077
	42 months preintervention	No Transformation	Numerator	Lag 0	34.981	14.451	2.421	0.039
	42 months postintervention	No Transformation	Numerator	Lag 0	-14.706	6.040	-2.435	0.038
ARIMA Model Parameters 9								
	Outcomes	No Transformation	Constant		82.125	47.140	1.742	0.115
			AR	Lag 1	-0.343	0.567	-0.605	0.560
	Phase	No Transformation	Numerator	Lag 0	-318.228	149.176	-2.133	0.062
	48 months preintervention	No Transformation	Numerator	Lag 0	34.982	14.450	2.421	0.039
	48 months postintervention	No Transformation	Numerator	Lag 0	-14.707	6.040	-2.435	0.038
ARIMA Model Parameters 10								
	Outcomes	No Transformation	Constant		82.121	47.139	1.742	0.115
			AR	Lag 1	-0.343	0.567	-0.605	0.560
	Phase	No Transformation	Numerator	Lag 0	-367.929	164.198	-2.241	0.052
	54 months preintervention	No Transformation	Numerator	Lag 0	34.983	14.450	2.421	0.039
	54 months postintervention	No Transformation	Numerator	Lag 0	-14.707	6.040	-2.435	0.038

Table 3. ARIMA model parameters for trimetazidine initiation in Figure 1B

ARIMA Model Parameters 1					Estimate	Standard error	t value	p value
Outcomes	No Transformation	Constant			776.317	103.231	7.520	< 0.001
		AR	Lag 1		-0.297	0.326	-0.910	0.386
Time period	No Transformation	Numerator	Lag 0		-118.993	31.738	-3.749	0.005
Phase	No Transformation	Numerator	Lag 0		-396.802	155.769	-2.547	0.031
Interact	No Transformation	Numerator	Lag 0		105.419	32.868	3.207	0.011
ARIMA Model Parameters 2								
Outcomes	No Transformation	Constant			776.291	103.227	7.520	< 0.001
		AR	Lag 1		-0.297	0.326	-0.911	0.386
Phase	No Transformation	Numerator	Lag 0		235.690	124.116	1.899	0.090
6 months preintervention	No Transformation	Numerator	Lag 0		-118.985	31.736	-3.749	0.005
6 months postintervention	No Transformation	Numerator	Lag 0		-13.573	12.070	-1.125	0.290
ARIMA Model Parameters 3								
Outcomes	No Transformation	Constant			776.294	103.228	70.520	< 0.001
		AR	Lag 1		-0.297	0.326	-0.911	0.386
Phase	No Transformation	Numerator	Lag 0		341.105	146.596	2.327	0.045
12 months preintervention	No Transformation	Numerator	Lag 0		-118.986	31.736	-3.749	0.005
12 months postintervention	No Transformation	Numerator	Lag 0		-13.574	12.070	-1.125	0.290
ARIMA Model Parameters 4								
Outcomes	No Transformation	Constant			776.297	103.228	7.520	< 0.001
		AR	Lag 1		-0.297	0.326	-0.911	0.386
Phase	No Transformation	Numerator	Lag 0		446.522	172.443	2.589	0.029
18 months preintervention	No Transformation	Numerator	Lag 0		-118.987	31.736	-3.749	0.005
18 months postintervention	No Transformation	Numerator	Lag 0		-13.574	12.070	-1.125	0.290
ARIMA Model Parameters 5								
Outcomes	No Transformation	Constant			776.301	103.229	7.520	< 0.001
		AR	Lag 1		-0.297	0.326	-0.911	0.386
Phase	No Transformation	Numerator	Lag 0		551.942	200.359	2.755	0.022
24 months preintervention	No Transformation	Numerator	Lag 0		-118.988	31.737	-3.749	0.005
24 months postintervention	No Transformation	Numerator	Lag 0		-13.574	12.070	-1.125	0.290

ARIMA Model Parameters 6								
	Outcomes	No Transformation	Constant		776.305	103.229	7.520	< 0.001
			AR	Lag 1	-0.297	0.326	-0.911	0.386
	Phase	No Transformation	Numerator	Lag 0	657.365	229.590	2.863	0.019
	30 months preintervention	No Transformation	Numerator	Lag 0	-118.989	31.737	-3.749	0.005
	30 months postintervention	No Transformation	Numerator	Lag 0	-13.574	12.070	-1.125	0.290
ARIMA Model Parameters 7								
	Outcomes	No Transformation	Constant		776.310	103.230	7.520	< 0.001
			AR	Lag 1	-0.297	0.326	-0.910	0.386
	Phase	No Transformation	Numerator	Lag 0	762.790	259.693	2.937	0.017
	36 months preintervention	No Transformation	Numerator	Lag 0	-118.991	31.737	-3.749	0.005
	36 months postintervention	No Transformation	Numerator	Lag 0	-13.574	12.071	-1.125	0.290
ARIMA Model Parameters 8								
	Outcomes	No Transformation	Constant		776.315	103.231	7.520	< 0.001
			AR	Lag 1	-0.297	0.326	-0.910	0.386
	Phase	No Transformation	Numerator	Lag 0	868.219	290.398	2.990	0.015
	42 months preintervention	No Transformation	Numerator	Lag 0	-118.992	31.737	-3.749	0.005
	42 months postintervention	No Transformation	Numerator	Lag 0	-13.574	12.071	-1.125	0.290
ARIMA Model Parameters 9								
	Outcomes	No Transformation	Constant		776.320	103.232	7.520	< 0.001
			AR	Lag 1	-0.297	0.326	-0.910	0.386
	Phase	No Transformation	Numerator	Lag 0	973.651	321.531	3.028	0.014
	48 months preintervention	No Transformation	Numerator	Lag 0	-118.994	31.738	-3.749	0.005
	48 months postintervention	No Transformation	Numerator	Lag 0	-13.574	12.071	-1.125	0.290
ARIMA Model Parameters 10								
	Outcomes	No Transformation	Constant		776.325	103.233	7.520	< 0.001
			AR	Lag 1	-0.297	0.326	-0.910	0.386
	Phase	No Transformation	Numerator	Lag 0	1079.087	352.980	3.057	0.014
	54 months preintervention	No Transformation	Numerator	Lag 0	-118.995	31.738	-3.749	0.005
	54 months postintervention	No Transformation	Numerator	Lag 0	-13.574	12.071	-1.125	0.290

A



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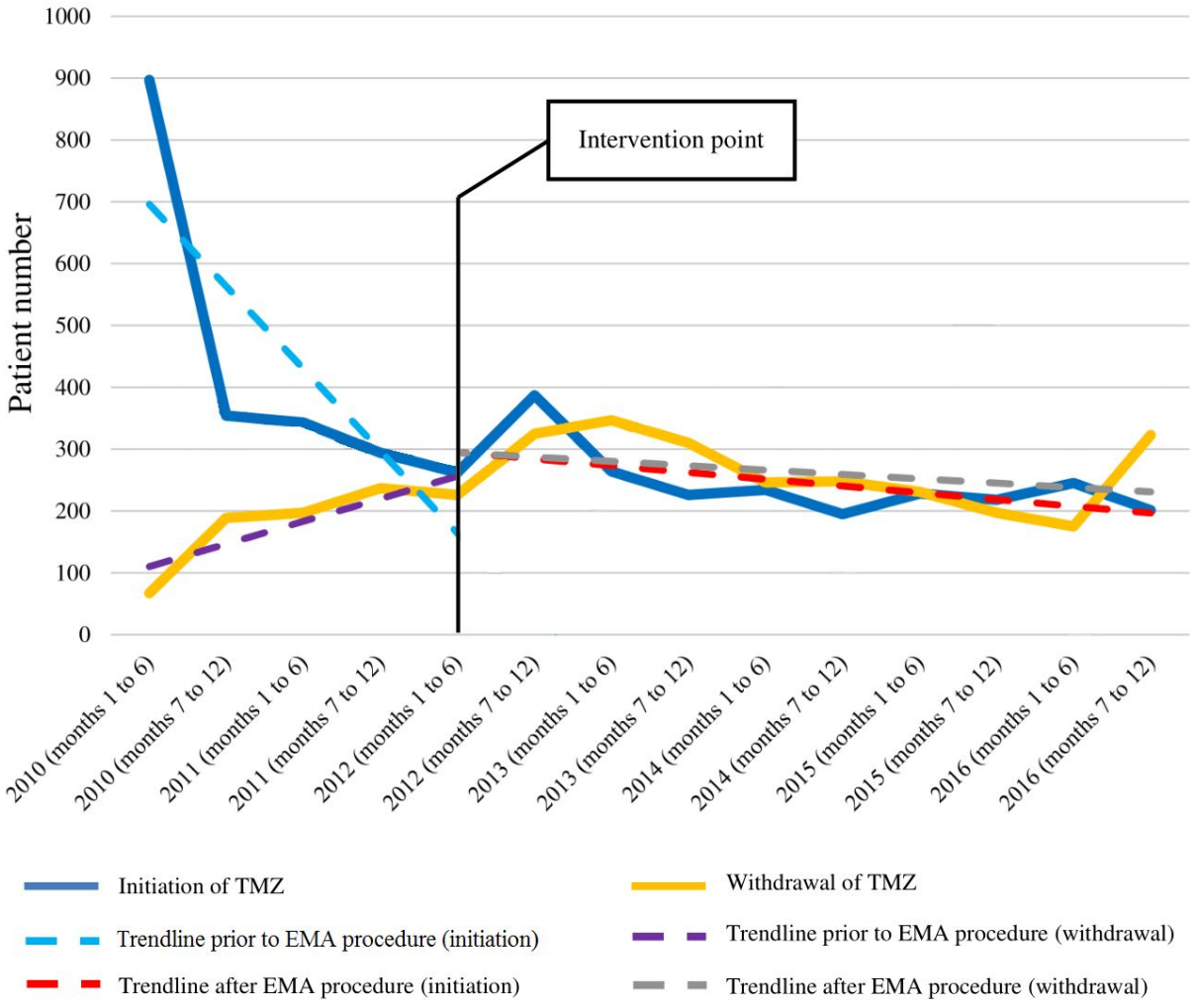

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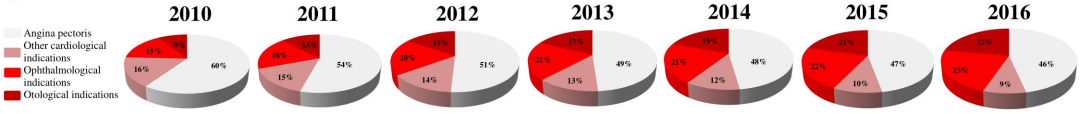
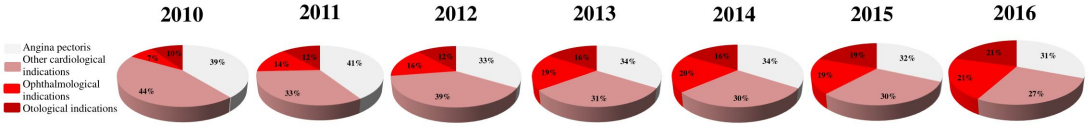


	2010	2011	2012	2013	2014	2015	2016
Number of patients	4248	4817	5287	5230	4749	4228	3433
Angina pectoris	2670	3447	3917	3994	3739	3434	2864
Other cardiological indications	724	955	1091	1072	900	736	543
Ophthalmological indications	683	1154	1511	1679	1679	1604	1389
Otological indications	405	794	1182	1433	1520	1518	1361

B



	2010	2011	2012	2013	2014	2015	2016
Number of patients	1251	637	649	490	429	446	446
Angina pectoris	453	323	284	244	223	221	231
Other cardiological indications	512	265	328	223	194	210	205
Ophthalmological indications	83	110	133	139	129	130	160
Otological indications	110	93	99	113	108	136	155