Switching the pharmaceutical dosage form of extended-release valproate is associated with therapeutic modification of antiepileptic therapy

Deutsches Arzneiprüfungsinstitut e.V.

Katrin Schuessel, PhD[1] (k.schuessel@dapi.de), Stephanie von Klot, PhD[2], and Martin Schulz, PhD[1,3]

[1]DAPI - German Institute for Drug Use Evaluation, 65760 Eschborn, Germany (www.dapi.de)

[2]Helmholtz Zentrum München, Institute of Epidemiology II, 85764 Neuherberg, Germany

[3]Drug Commission of German Pharmacists (AMK), 10117 Berlin, Germany.

Publication # 516

Background

Product switching or generic substitution of extended release (ER) antiepileptic drugs (AED) is discussed controversially since evidence from bioequivalence studies may not translate into clinical practice.

Objectives

To explore whether two different aspects of product switching,
- switching the pharmaceutical manufacturer and / or
- switching the **pharmaceutical dosage form (monolithic vs multi-unit)**

in patients treated with ER valproic acid/valproate (VPA)

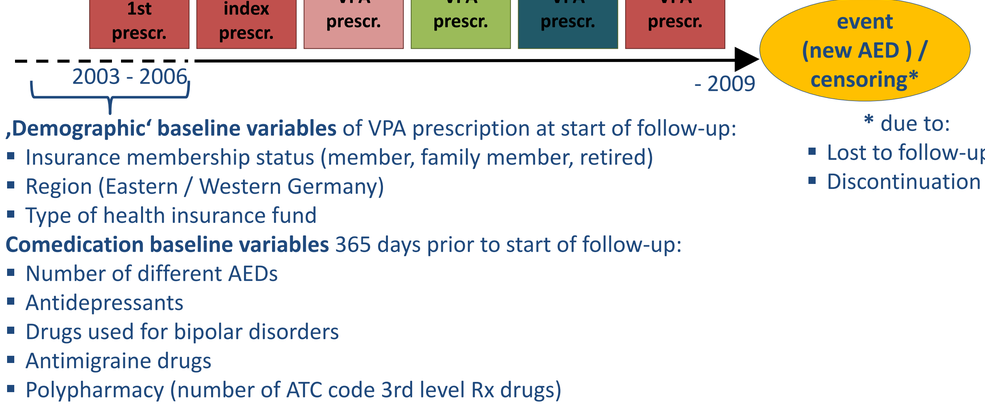
is associated with therapeutic modification of AED therapy, i.e. prescribing of an additional AED as a proxy for treatment failure e.g., due to side effects or compromised effectiveness.

Methods

Design and setting:
- DAPI drug claims database (www.dapi.de)
- Statutory health insurance patients
- > 80 % of German community pharmacies
- Retrospective cohort study
- New users of ER VPA
- No VPA in year before first prescription
- Filling a second prescription (index) within 180 days

Statistical analysis:
- Extended Cox proportional hazards regression modelling with time-varying exposure
- Significance level : $p < 0.01$
- R Version 2.14.1.

Time-dependent VPA exposure:
- VPA product switch (‚generic substitution')
- Type of pharmaceutical dosage form (**monolithic** vs **multi-unit**)
- Medical specialty of prescriber
- Dosage strength



‚Demographic' baseline variables of VPA prescription at start of follow-up:
- Insurance membership status (member, family member, retired)
- Region (Eastern / Western Germany)
- Type of health insurance fund

Comedication baseline variables 365 days prior to start of follow-up:
- Number of different AEDs
- Antidepressants
- Drugs used for bipolar disorders
- Antimigraine drugs
- Polypharmacy (number of ATC code 3rd level Rx drugs)

Figure 1: Study design.

Results I: Study cohort

- **78,427 medication profiles included**
  - **15,065 (19.2 %) experienced the event (prescription of new AED)**
- **106,150 years total follow-up time**
  - 6,567 years (6.2 %) with change of pharmaceutical manufacturer
  - periods with switch of pharmaceutical dosage form are rare:
    - 809 years (0.76 %) **multi-unit** → **monolithic**
    - 819 years (0.77 %) **monolithic** → **multi-unit**
    - 77 years (0.07 %) combination → one type
    - 94years (0.09 %) one type → combination

Table 1: Further characteristics of study cohort.

	Number (%) of medication profiles
Pretreated with further antiepileptic drugs (AED)	26,267 (33.5)
Insurance membership status:	
Member	31,977 (40.8)
Family member	16,297 (20.8)
Retired	30,153 (38.4)
Index prescription by pediatrician	6,241 (8.0)
Number of ATC-code 3rd level Rx drugs:	
0-4	16,055 (20.5)
5-9	16,971 (21.6)
10-14	13,635 (17.4)
15-23	16,239 (20.7)
≥ 24	15,527 (19.8)
Pretreated with neuroleptics for bipolar disorders	18,613 (23.7)
Pretreated with antidepressants	33,437 (42.6)
Pretreated with antimigraine drugs	4,888 (6.2)

Results II: Outcome measures

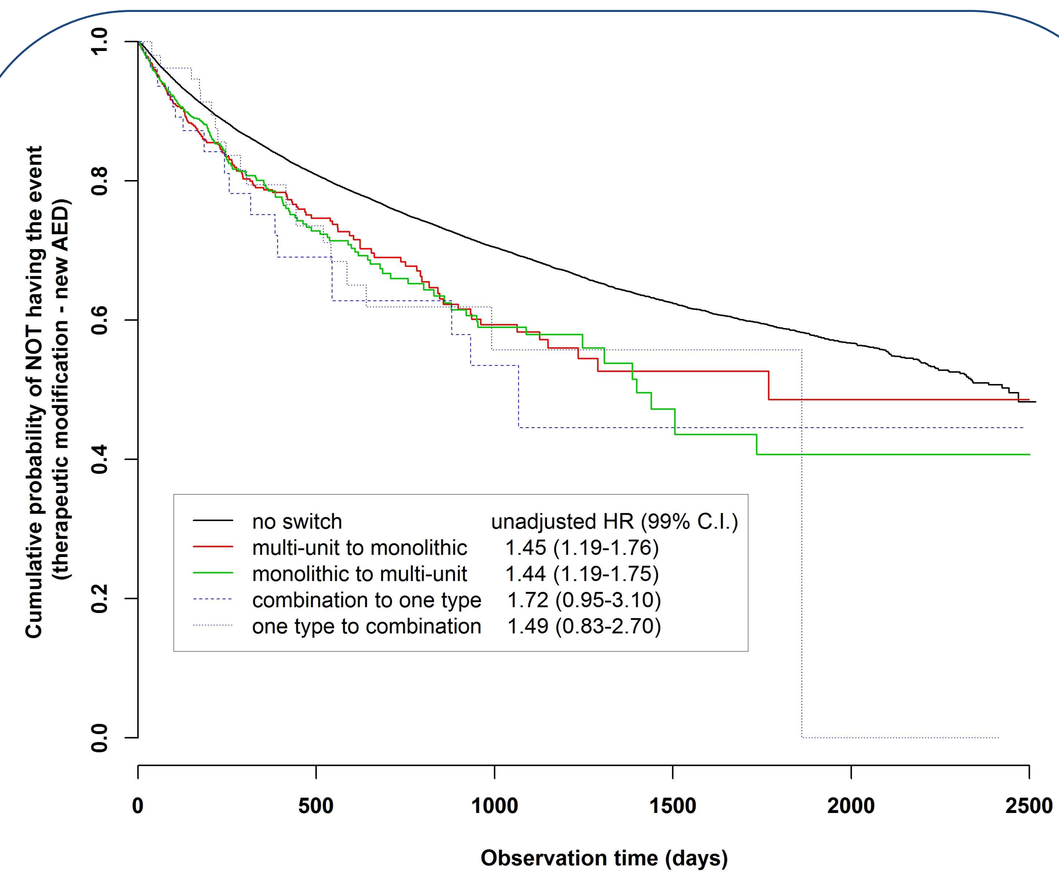


Figure 2: Kaplan-Meier curves for pharmaceutical dosage form switches.

Table 2: Results of multivariate Cox proportional hazards models: HR for therapeutic modification – new AED (adjusted for all available covariates).

	HR (99 % C.I.)
Switch of pharmaceutical manufacturer (ref. no switch)	**1.01 (0.92 – 1.12)**
Switch of pharmaceutical dosage form (ref. no change)	
• **multi-unit → monolithic**	**1.43 (1.16 – 1.77)**
• **monolithic → multi-unit**	**1.36 (1.10 – 1.67)**
• **combination → one type of dosage form**	**1.75 (0.96 – 3.20)**
• **one type of dosage form → combination**	**0.80 (0.39 – 1.66)**
Number of ATC-code 3rd level Rx drugs (ref. 0-4)	
5-9	1.11 (1.03 – 1.19)
10-14	1.23 (1.14 – 1.34)
15-23	1.36 (1.26 – 1.47)
≥ 24	1.93 (1.78 – 2.09)
Pretreated with neuroleptics for bipolar disorders	0.78 (0.74 – 0.82)
Pretreated with antidepressants	1.07 (1.02 – 1.12)
Pretreated with antimigraine drugs	1.18 (1.08 – 1.27)

Conclusions

- Switching of ER VPA products is associated with an increased risk of AED regimen modification.
- The type of pharmaceutical dosage form is probably more influential than differences between pharmaceutical manufacturers.
- **Switching extended-release valproic acid products (and especially the type of pharmaceutical dosage form) solely due to economic considerations may be disadvantageous.**

Limitations / Open questions

- Bias from unmeasured confounding
- Surrogate endpoint (insensitive?) → bias towards the null (?)
- Association vs causality
- Possible explanations:
  - Pharmacokinetic differences
  - Psychological factors

Conflict of interests

- This study was not financially supported by an external organization or a pharmaceutical company, i.e. the research proposal, study protocol, data acquisition, analysis and interpretation of data was the sole responsibility of the authors.
- Since 2011, SvK is an employee of Boehringer Ingelheim Pharma GmbH & Co. KG , Ingelheim, Germany.