Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Author reply to technical comment | Published 19 February 2021 | doi:10.4414/smw.2021.20481
Cite this as: Swiss Med Wkly. 2021;151:w20481

Valproate in pregnancy: authors' reply

Reply to comment on: Use of valproate in pregnancy and in women of childbearing age between 2014 and 2018 in Switzerland: a retrospective analysis of Swiss healthcare claims data

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We would like to thank Prof. von Mandach and Prof. Hösli for their interest in our study and for raising some important points [1]. We support the efforts by SAPP to provide guidelines on the use of drugs during pregnancy, as well as by the Swiss Teratogen Information Service (STIS) initiative, which prospectively collects information on a case basis to inform healthcare providers on drug exposure during pregnancy in Switzerland. We are convinced that drug utilisation studies like ours benefit such efforts by highlighting the areas of greatest medical need in this under-investigated patient population.

Prof. von Mandach and Prof. Hösli highlight several limitations of Swiss healthcare claims databases, such as the lack of information on outpatient diagnoses (i.e., the underlying indication for drug use), the lack of information on adherence to drug therapy, as well as the the lack of information of drug dosage. As for any type of research, it is important to consider such limitations when framing the study question in observational database research, because not every question can be studied in every data source. Nevertheless, we feel strongly that the absence of such information should not prevent the use of such longitudinal and representative databases, which have become an established data source for drug utilisation studies wordwide. Healthcare claims databases are the only available data source in Switzerland that capture dispensed drugs representatively for the overall population and longitutinally over time. It is correct that specific epilepsy pregnancy registries (e.g., the international EURAP or North American NAADPR) document indications for antiseizure medications, drug dosages, and pregnancy outcomes in the mother and the child in much more detail than claims databases. However, the populations enrolled in such registries are highly pre-selected, because women have to actively enroll themselves (NAADPR) or have to be enrolled by their treating specialist/epileptologist (EURAP) [2]. Thus, while such registries can provide excellent information on birth outcomes and details on drug use, they cannot provide representative and population-based evidence on drug utilisation [2]. Studies like ours have to be seen as complementary to such registry-based studies, whereby each type of study contributes different important and valid information to the bigger picture [2].

As Prof. von Mandach pointed out, Denmark and other Scandinavian countries have invested in building elaborate national birth registries to capture data on all pregnancies in the country [3]. These registries can be linked to national healthcare claims databases and other national health registries. Such efforts have been part of a strong national focus on public health measures in Scandinavia over decades and are embedded in a centralised national health system. Although desirable, a comparable birth/pregnancy registry has not been established in Switzerland to date, and the use of representative data to monitor drug utilisation in vulnerable patient populations has not been promoted on an institutional level in the past. We hope that our study highlights the benefits of using pre-existing electronic health data to representatively evaluate drug utilisation in Switzerland, and we hope that studies like ours support the integration of such research into national public health efforts. Of course, it will be important to collect and analyse representative data in a way that is compatible with the Swiss decentralised healthcare system, which is very different from Scandinavian healthcare systems. Helsana is one of the largest health insurance companies in Switzerland, but nevertheless it still "only" covers approximately 15% of a relatively small Swiss population; therefore the sample size is small for evaluation of rare exposures. As discussed in the manuscript, this is the reason why we cannot provide unweighted absolute results of our study for confidentiality reasons. A national electronic patient dossier would be highly desirable in order to better evaluate several health

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source: https://doi.org/10.48350/154668 | downloaded: 12.10.2024

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aspects on a population-based level in Switzerland, but at the moment, it seems unlikely that it will be implemented in the near future. Furthermore, it will take a long time for such an electronic dossier to achieve a large enough sample size and long enough follow up.

Finally, we would like to clarify one important point raised. It is true that the start of pregnancy is not recorded in healthcare claims databases, as this is not an event that is billed to health insurers. This is a limitation that is common to all claims databases worldwide. Nevertheless, healthcare claims databases have become an established tool to evaluate drug use and safety during pregnancy, and estimation of the last menstrual period to approximate the start of pregnancy has been validated in several peer-reviewed publications and is common practice in this field of research [4–8]. It is correct that first trimester ultrasound is a more exact method to determine actual gestational age, but although health insurance reimburses this examination, actual information on the exact gestational age determined by the ultrasound is not recorded in health insurance data. In theory, the claim for the examination should be indicative of the 12th or 13th week of pregnancy. However, in practice this point in time can vary, depending on factors such as whether or not a pregnancy is considered "high-risk" and is thus affected by larger inaccuracies. Additionally, first-trimester ultrasounds are usually reimbursed as a bundeled TARMED payment for a prenatal visit.

We thank our colleagues for their interest in our work and we look forward to contributing evidence to benefit pregnant women in Switzerland in synergy with efforts by SAPP and the STIS.

Disclosure statement

The original study was supported by the Swiss RBP IV fund for health quality and patient safety. The authors declare no conflict of interest.

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