**An-Najah National University**

**Faculty of Graduate Studies**

# PHARMACOTHERAPY OF EPILEPSY IN WOMEN: CURRENT STATUS, FUTURE DIRECTIONS, AND CHALLENGES

**By**

**Lina Azmi Mostafa Zaid**

**Supervisor**

**Dr. Ramzi Shawahna**

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Lina Azmi Zaid

This Thesis was Defended Successfully on 31/03/2022 and approved by

| | |
|---|---|
| Ramzi Shawahna<br>Supervisor | Signature |
| Firas Bazzari<br>External Examiner | Signature |
| Naim Kittana<br>Internal Examiner | Signature |

## Dedication

الى من علمني ان الدنيا كفاح ..... وسلاحها العلم والمعرفة

الى من حصد الاشواك عن دربي..... ليمهد لي طريق العلم

والدي العزيز

الى من ساندتني في صلاتها ودعائها ..... الى من سهرت الليالي تنير دربي

الى اجمل ابتسامة في حياتي ..... الى اروع امرأة في الوجود

امي الغالية

الى رفيق دربي ..... وشريك حياتي

الى من انار طريقي ..... الى منبع الحب والعطاء

زوجي العزيز

الى القلوب الطاهرة والرقيقة ..... الى النفوس البريئة

الى من حبهم يجري في عروقي ..... ويلهج بذكراهم فؤادي

اولادي وفلذات كبدي

انس, محمد, تالا

لينا عزمي مصطفى زيد

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- Thanks also to appreciate the efforts of all respected teachers and staff of Pharmacology Department at An-Najah National University.

## Declaration

I, the undersigned, declare that I submitted the thesis entitled:

**PHARMACOTHERAPY OF EPILEPSY IN WOMEN: CURRENT STATUS, FUTURE DIRECTIONS, AND CHALLENGES**

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

**Student's Name:** Lina Azmi Zaid

**Signature:** Lina Zaid

**Date:** 31/03/2022

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**PHARMACOTHERAPY OF EPILEPSY IN WOMEN: CURRENT STATUS, FUTURE DIRECTIONS, AND CHALLENGES**

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**Dr. Ramzi Shawahna**

# ABSTRACT

**Background:** This study was conducted in two phases: a systematic review and a qualitative study. The systematic review was conducted to evaluate concentrations of antiepileptic drugs (AEDs) in breastmilk of lactating women with epilepsy (WWE). The qualitative study was conducted to explore the perspectives of neurologists, gynecologists, psychiatrists, internists, and pharmacists about caring for WWE in Palestine.

**Methods:** In the systematic review, the databases: MEDLINE/PubMed, EMBASE, CINAHL/EBSCO, COCHRANE, SpringerLink, ScienceDirect, Summon, WHO International Clinical Trials Registry Platform, and SCOPUS were systematically searched. In the qualitative study, a purposive sampling technique was used to recruit the participants for the qualitative study. Semi-structured in-depth interviews were conducted neurologists (n = 6), gynecologists (n = 5), psychiatrists (n = 3), internist (n = 1), and clinical pharmacists (n = 5). The interpretive description methodology was used to thematically analyze the qualitative data. Estimated daily intake (EDI) and relative infant doses (RID) of AEDs were calculated.

**Results:** A total of 15 records were included in this systematic review. The included studies reported levels of 8 AEDs in the breastmilk of WWE. Lamotrigine, levetiracetam, carbamazepine, topiramate, valproic acid, and gabapentin did not produce significant adverse effects that warranted discontinuation of breastfeeding. The mean EDI of AEDs ranged from 0.1 to 278.16 µg/g body weight/day and the mean RID ranged from 1.63% to 36.33%. Breastfeeding might be limited or even discontinued when signs of excessive sedation/drowsiness and/or poor weight gain are evident in infants exposed to primidone and phenobarbital, ethosuximide/primidone, or ethosuximide/phenobarbital. The following themes emerged from the qualitative data: 1) diagnosis and care for patients with epilepsy, 2) general issues in caring for patients

with epilepsy, and 3) consideration of women's issues in the pharmacotherapy of epilepsy.

**Conclusion:** Healthcare providers and WWE might use the findings of this study to make informed decisions on the safety of breastfeeding while taking AEDs. Findings of this qualitative study showed a need to formally adopt uniform guidelines that can guide the diagnosis and care of WWE in the Palestinian healthcare system.

**Keywords:** Antiepileptic drugs, Breastfeeding, Epilepsy, Human milk, Lactation, Women

# Chapter One

# Introduction and Theoretical Background

## 1.1 Introduction

Epilepsy is one of the most common chronic neurological conditions worldwide that is characterized by unprovoked recurrent seizures (1). Globally, epilepsy affects more than 65 million individuals (2). The prevalence of epilepsy among women was estimated at 6.85 cases per 1,000 women (2-5). It has been estimated that approximately 50% of women with epilepsy (WWE) were of childbearing age (15-49 years). Today, approximately 15 million women of childbearing age are affected by epilepsy around the globe (6, 7). In clinical practice, the pharmacotherapy of WWE can be challenged by several women-related issues (8). Both epilepsy and antiepileptic drugs (AEDs) can have implications on the menstrual cycle, menopause, contraception, reproduction, pregnancy, birth outcomes, and breastfeeding (8).

Human breastmilk is the recommended form of enteral feeding for all infants including preterm infants (9). Breastfeeding has many health benefits for the infant and the mother. These benefits include prevention of infections, promotion of development, and psychological attachment between the mother and her infant (10). However, medications including AEDs excreted in breastmilk could present a source of exposure to breastfed infants. This exposure could be associated with adverse effects (11). Breastfeeding is a serious concern for WWE of childbearing age and their providers of care (12). As the majority of WWE achieve adequate control over their seizures using AEDs, discontinuing these AEDs during breastfeeding could be associated with serious threats to the wellbeing of WWE and their infants (13). Healthcare providers are frequently asked if WWE can breastfeed while taking AEDs. Recent position papers and guidelines encouraged WWE to breastfeed because the benefits of breastfeeding outweigh the potential adverse effects caused by infant exposure to AEDs (6, 12-15). It is noteworthy mentioning that risk assessment of infant exposure to AEDs via breastmilk would be of great interest to healthcare providers who need to counsel lactating WWE on breastfeeding.

Even though epilepsy affects both men and women equally, it is generally accepted that being a woman with epilepsy is very different from being a male with epilepsy (16). Several gender-related factors can make caring for WWE, especially those of childbearing age, challenging to the healthcare professionals and WWE themselves (8, 17-21). These issues include teratogenicity, lactation, the effect of hormones on seizures, menstrual cycle, aspects of contraception, sexuality, bone health, and many others (18, 22). Studies have shown that the frequency of seizures increases in about one-third of WWE in the premenstrual and/or preovulatory periods (23). Additionally, the incidence of congenital malformations was estimated at 6% among WWE who use AEDs which was significantly higher than that among the general population (24). The use of valproic acid was associated with menstrual irregularities, changes in hormonal functioning, and an increased risk of polycystic ovary syndrome (25). Therefore, it is recommended that some AEDs like valproic acid might be avoided in WWE of childbearing age (26).

### 1.2 Concentrations of antiepileptic drugs in breast milk

Several studies were conducted to examine concentrations of AEDs in human breastmilk. A recent study was conducted by Kacirova et al. to evaluate concentrations of lamotrigine in breastmilk and serum of both mothers and their infants in the first month after delivery (27). The study showed a significant correlation between concentrations of lamotrigine in serum and breastmilk of the mothers and the serum of their infants. Another study by Paulzen et al. assessed levels of lamotrigine in blood, umbilical cord, amniotic fluid, and breastmilk samples from WWE (28). Lockwood et al. quantified concentrations of pregabalin in breastmilk samples from WWE and assessed infant exposure to pregabalin via breastmilk (29). The study estimated that infants were exposed to pregabalin at a dose of 0.31 mg/kg/day. In another study, Newport et al. quantified concentrations of lamotrigine in breastmilk, maternal plasma, and plasma of breastfed infants (30). The study reported breastmilk/plasma ratios of lamotrigine and compared levels of lamotrigine in the maternal plasma and their infants. Other studies were conducted to quantify concentrations of levetiracetam and topiramate in biological fluids of breastfeeding WWE and their infants (31-33).

### 1.3 Caring for women with epilepsy

Several guidelines for caring for WWE were previously published (3, 8, 14, 34). Many previous studies have reported a lack of knowledge of women's issues in epilepsy among healthcare professionals (18, 35-37). Similarly, studies reported a lack of adherence to guidelines of caring for WWE. In Palestine, Shawahna et al. reported gaps of knowledge relevant to women issues in epilepsy among practicing pharmacists (18). Similarly, gaps of knowledge were also identified among physical educators, physiotherapists, future physicians, and nurses in Palestine (38-41). In Denmark, Daugaard et al. reported an increase in using AEDs among Danish women of childbearing age during the period from 2001 to 2016 (42). Analysis of the prescription trends showed an increase in using lamotrigine and a decline in using valproate among pregnant women and women of childbearing age. In Australia, an analysis of 508 pregnant WWE who received multiple AEDs showed that using valproate and topiramate were associated with an increased incidence of congenital malformations (43). The study concluded that lamotrigine and levetiracetam were associated with lower rates of congenital malformations. In another study, an analysis of 580 pregnant WWE showed that decreasing doses of valproate reduced the risks of fetal abnormalities (44). In another analysis, intrauterine exposure to AEDs increased the risk of fetal death during pregnancy (45). Keni et al. analyzed data from the Kerala Registry of Epilepsy and Pregnancy to investigate changes in the usage of folic acid, AEDs, seizures during pregnancy, and the rate of congenital malformation over a course of two decades (46). The study showed that seizure control and the use of high doses of folic acid during pregnancy improved over the two decades. On the other hand, the rates of congenital malformation remained unchanged due to the continued use of valproate, topiramate, and clobazam (46).

### 1.4 Caring for women with epilepsy in Palestine

Palestinians receive healthcare from three main providers: the government, the private sector, and the United Nations Relief and Works Agency (UNRWA) for Palestine Refugees in the Near East. Local protocols, guidelines, and policies for the diagnosis and management of patients with epilepsy in Palestine were not developed/adopted before (47). In routine practice, patients who experience a first seizure would be rushed to an emergency room/unit. After receiving emergency/ambulatory care by internal

medicine specialists, the patients would be referred to neurology services. In neurology services, patients would be examined by a neurologist who would make a final diagnosis based on physical/clinical examination, laboratory tests, and neuroimaging reports. It is noteworthy mentioning that the Palestinian healthcare system is short with neurologists. According to a recent report from the Palestinian Economic Policy Research Institute, there were approximately 1.45 neurologists for every 100,000 Palestinians. Therefore, patients with epilepsy have limited access to neurology services (4, 48). Patients with psychiatric comorbidities are scheduled to see a psychiatrist. Pregnant WWE and those with gynecological issues are referred to gynecologists. It is noteworthy mentioning that the majority of patients with epilepsy in the Palestinian healthcare system are prescribed AEDs by specialists. Because some AEDs have abuse potential, general practitioners are not allowed to prescribe AEDs. Eligible patients who have valid prescriptions can obtain their monthly supplies of AEDs at subsidized prices from the dispensaries of the Palestinian Ministry of Health. These dispensaries are run by qualified pharmacists. Dispensaries are often short with safe AEDs for pregnant WWE and those of childbearing age like lamotrigine and levetiracetam. Therefore, WWE often need to purchase these AEDs from privately owned pharmacies and pay out-of-pocket. Despite the availability of different generics, many WWE cannot afford the high costs of these AEDs (49).

### 1.5 Problem Statement

Although many studies have quantified concentrations of AEDs in breastmilk of lactating WWE (28, 50-55), a systematic review examining concentrations of AEDs and assessing risks to the exposed infants was not conducted before.

In modern healthcare delivery, caring for WWE, notably those of childbearing age, is regarded as collaborative work between healthcare providers including neurologists, gynecologists, internists, and clinical pharmacists. Such collaboration is critical for improving pharmacotherapy, support, and quality of life of WWE. Additionally, efforts to benchmark and improve healthcare delivery to patients with epilepsy have been surmounting on a global level (20, 56, 57). In a previous study in Palestine, key performance indicators that could be used in capturing and measuring pharmaceutical care services for patients with epilepsy were developed (20). In another study, the unique challenges faced by providers of perioperative care to patients with epilepsy

were explored (47). Currently, little is known about the current status of care received by WWE. Additionally, little is known on what challenges the provision of optimal care for WWE in Palestine. Moreover, little is known on the future directions that can be used to guide improving care of Palestinian WWE.

## 1.6 Study Purpose

This study was conducted in two phases: a systematic review and a qualitative study. The systematic review was conducted to evaluate concentrations of AEDs in breastmilk of lactating WWE. The other aims of this review were to qualitatively synthesize evidence that can be used to estimate theoretical doses as estimated daily intake (EDI) of AEDs, relative infant doses (RID or %RID), and to evaluate the potential risks to infants as a result of exposure to AEDs via breastmilk. The findings of this review might help healthcare providers and WWE make informed decisions on the safety of breastfeeding while taking AEDs. On the other hand, the qualitative study was conducted to explore the current status of caring for WWE, key challenges, and future directions of caring for WWE from the perspectives of healthcare professionals who provide care for WWE in Palestine.

## 1.7 Significance of the Study

Caring for WWE of childbearing age requires a collaborative partnership between neurologists, internists, gynecologists, and pharmacists. Such collaborative partnership is essential for protecting WWE of childbearing age from unintended pregnancies, complications during pregnancy (including teratogenic effects, major congenital malformation, subtherapeutic levels of AEDs, and risk of seizure breakthrough), and to minimize negative side effects of their treatment and could improve quality of life of WWE.

# Chapter Two

# Methods

This study was conducted in two phases:

## 2.1 Phase 1: Systematic review of the literature

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42020223645. Additionally, this systematic review was conducted and reported in adherence to the preferred reporting items for systematic review and meta-analysis (PRISMA) statement (58). Adherence to the PRISMA checklist is shown in Appendix A. This review followed the Joanna Briggs Institute (JBI) methodology for systematic reviews of etiology and risk (59).

### 2.1.1 Preliminary search

We conducted a preliminary search in the following databases: PROSPERO, the Cochrane Database of Systematic Reviews, the JBI Database of Systematic Reviews and Implementation Reports, and PubMed/MEDLINE to identify recent and/or registered systematic reviews on concentrations of AEDs in human breastmilk. Current and/or underway systematic reviews were identified.

### 2.1.2 Review questions

The review questions were: a) what are the concentrations of different AEDs excreted into breastmilk of lactating WWE who are taking AEDs? b) can these concentrations be used to estimate theoretical doses received by infants who are breastfed by WWE taking AEDs? c) can these concentrations be used to evaluate the potential risks to infants as a result of exposure to AEDs via breastmilk? and d) what are the reported infant risks associated with the doses of AEDs received by infants via breastmilk?

### 2.1.3 Participants

This review considered studies that included lactating WWE who were taking AEDs. Studies were included regardless of the race, place of residence, parity, nutritional, and socioeconomic status of the WWE who donated the samples.

### 2.1.4 Exposure of interest

The exposure was receiving AEDs by WWE. In this study, we were interested in the concentrations of AEDs excreted into breastmilk of lactating WWE who received AEDs. The potential comparator (if any) was another cohort of women who did not receive AEDs during the lactation period that has been previously studies.

### 2.1.5 Primary outcome

The primary outcome in this study was the concentrations of AEDs excreted into breastmilk of lactating WWE who received AEDs. Studies were included if they measured and reported breastmilk levels of AEDs.

### 2.1.6 Secondary outcomes

Concentrations of AEDs in blood, plasma, serum, and/or umbilical cord blood were secondary outcomes of interest. Another secondary outcome of interest was the adverse effects reported among the infants who were exposed to AEDs via breastmilk.

### 2.1.7 Confounding factors

Type of epilepsy/seizures, doses of the AEDs, the frequency at which the AEDs were administered, analytical methods used to quantify concentrations of AEDs, time points at which the biological samples were collected, lactation period, type of breastmilk collected, methods of breastmilk collection, sample handling methods, sample preparation methods were potential confounding factors that were considered when comparing the study outcomes. When the potentially confounding factors were reported, their effects were compared across studies in the cases included and in those used as controls (if any). Breastmilk concentrations of AEDs were used as the comparative outcome between the studies. It is important to note that differences in the type of breastmilk used (foremilk and hindmilk) proved difficult to compare. Therefore, we focused on measuring and comparing the levels of AEDs in breastmilk samples as translated in units of mass per unit of volume (concentrations).

### 2.1.8 Types of studies

In this review, observational studies of different study designs were eligible for inclusion: prospective cohort studies, retrospective cohort studies, case-control studies, time-series studies, and analytical cross-sectional studies.

### 2.1.9 Search strategy

In this review, the search strategy aimed to identify published and unpublished data. An initial search was conducted through MEDLINE/PubMed, Springer Link, COCHRANE, and Science Direct to identify relevant articles on the topic. We used the terms and text words used in the titles, abstract, and keywords of the identified articles in addition to the key terms and Medical Subject Headings (MeSH) used to index these articles to develop the full search strategy to be used in this review. The Boolean operators "AND" and "OR" were used to combine the key terms. The databases were searched as late as May 15, 2021. An example of the search strategies adopted for one of the databases is presented in Appendix B.

### 2.1.10 Information sources

The search strategy was customized for the following databases: MEDLINE/PubMed, EMBASE, CINAHL/EBSCO, COCHRANE, SpringerLink, ScienceDirect, Summon, WHO International Clinical Trials Registry Platform, and SCOPUS (39, 57, 60, 61). The search engine Google Scholar was used to search additional data that might be published as academic theses/dissertations and government reports (gray literature). References of the identified studies that were selected for quality appraisal were searched manually to detect if there were additional studies that could be included in this review. We did not restrict the search to a particular article type, publication type, study type, and/or publication status. We filtered the results for human studies and those published in English due to the limited translation resources.

### 2.1.11 Study selection

After the search, the identified citations were imported as Research Information Systems (RIS) and Comma-Separated Values (CSV) files. The RIS files were collated and uploaded into EndNote v.X7 (Clarivate Analytics, Philadelphia, PA) and the CSV files were collated and uploaded into Microsoft Excel (Microsoft Inc. 2017). Duplicate citations were removed. Removing the duplicates was repeated to ensure reproducibility. Two researchers (LZ and RS) independently screened the titles and abstracts of the remaining citations against the inclusion criteria. Both researchers discussed discrepancies and resolved them. In case of discrepancies were not resolved, help was sought from a third researcher for consensus. Two researchers independently

assessed the full text of the selected citations against the inclusion criteria in detail. In case a full text was excluded, the reason for exclusion was recorded by both researchers and the results were reported in the systematic review.

### 2.1.12 Assessment of methodological quality

Both researchers critically appraised the methodological quality of the selected citations to be included in the review independently. The relevant assessment and appraisal tools depended on the type of study selected. The JBI Critical Appraisal Checklists for cross-sectional studies, cohort studies, and case series were used (59).

### 2.1.13 Data extraction

The data were extracted into a standardized data collection tool similar to those used in JBI SUMARI (59). In addition to the main outcome of interest (breastmilk levels of AEDs), data relevant to the dose, frequency, route of administration of the AEDs were collected. Information relevant to the WWE from which the samples were collected like age, parity, place of residence, type of epilepsy, lactation period, other health conditions were recorded whenever reported. Data relevant to the sample collected like the type of breastmilk, collection, handling, preparation, and analytical method were also noted when reported. We also collected data relevant to the citation like name(s) of the author(s), year of publication, journal in which the study was published, setting and/or country where the study was conducted, aims/objectives of the study, design of the study, and funding information. The data were extracted by two researchers independently. The data extraction form is shown in Appendix C. Missing or incomplete data were collected by contacting the corresponding author through email or phone. Both researchers made this contact. If the contact failed, we used the available data for analysis. In the meantime, the effect of these missing data was discussed.

### 2.1.14 Data synthesis

Attempts were made to pool quantitative data relevant to breastmilk, maternal blood/plasma/serum, infant blood/plasma/serum levels of AEDs across the different studies in statistical meta-analysis. Due to the very heterogenous nature of the studies, a qualitative synthesis was adopted in this study. Breastmilk, maternal blood/plasma/serum, infant blood/plasma/serum levels of AEDs were presented in

tables. Theoretical doses were calculated as EDI of AEDs using the following equation (1) (62):

$$\text{EDI} = \frac{\text{C X BMI per 24h}}{\text{Wt}} \quad (1)$$

Where EDI was the estimated daily intake of AED, C was the concentration of the AED in breastmilk, BMI was the breastmilk intake per 24 h, and Wt was the body weight of the breastfed infant.

In addition to the EDI, RID or %RID was calculated as a useful comparative parameter to assess the amount of AED received by the infants via breastmilk (63-66). The RID is the ratio (%) of the weight-adjusted infant dose of AED per time that is received via breastmilk relative to the maternal dose over the same period on a body weight basis. Because the therapeutic doses of AEDs in neonates and/or infants were not available, the maternal weight-adjusted doses were alternatively used. The RID values were calculated using equation (2) (63-66):

$$\text{RID} = \frac{\text{Infant daily dose per kg via breastmilk}}{\text{Maternal daily dose per kg}} \text{ X } 100 \quad (2)$$

The infant dose received via breastmilk was calculated from the average concentration of the AED in breastmilk multiplied by the amount of breastmilk intake (150 mL/kg/day) (63-66). When the RID was 100%, this indicated that the infant dose received via breastmilk was equal to the maternal therapeutic dose per weight. In clinical practice, a RID value of 5 to 10% was considered as a safety threshold for risk assessment (63).

The molecular descriptors, physiochemical, and pharmacological/pharmacokinetic properties of the AEDs like the molecular mass, polar surface area, n-octanol–water partition coefficient (logP), pKa, Lipinski's rule of five, human intestinal absorption, oral bioavailability, ability to cross the blood-brain barrier, protein binding, volume of distribution, and elimination half-life were obtained from DrugBank (release v. 5.1.9) (67-71).

## 2.2 Phase 2: Qualitative study

### 2.2.1 Design of the study

A qualitative explorative design was used in this study in adherence to the COnsolidated Criteria for REporting Qualitative Research (COREQ) checklist (72). The study participants were interviewed in semi-structured in-depth interviews using a pre-validated and pilot-tested interview schedule. The interview schedule is provided in the Appendix D. All interviews were conducted in the period between March and September 2021. As the study was conducted during the ongoing COVID-19 pandemic, physical distancing was practiced during the interviews.

## 2.3 Recruitment of the interviewees

In the Palestinian healthcare system, patients with epilepsy including WWE often receive care from neurologists, gynecologists, psychiatrists, internal medicine specialists, and clinical pharmacists. Therefore, it was decided to interview healthcare providers from these specialties in this study. Because being knowledgeable of the issue being investigated is a prerequisite for generations of rich qualitative data, a judgmental sampling technique was used to recruit the interviewees in this study (73-76). The interviewees in this study were identified, invited, and recruited using personal contacts in the field. The following inclusion criteria were used in this study: 1) having a license to practice in Palestine, 2) being in practice for at least 5 consecutive years, 3) caring for patients with epilepsy including WWE, and 4) providing informed consent to participate in a recorded interview (73-76).

## 2.4 The number of interviews required for this study

The number of interviews required for this study was estimated using thematic saturation as an endpoint. Although this method was adaptive, the number of interviews required for this study was determined a priori. We estimated that thematic saturation would be achieved in 10 h of interview time. Assuming a median interview time of about 40 min, at least 15 interviews were required to generate sufficient qualitative data to saturate the main themes and subthemes (47, 74, 75).

### 2.5 Development of the interview schedule and collection of the qualitative data

The interview schedule used in this study was developed after a preliminary search and review of the peer-reviewed literature (77-79). To explore the perspectives of the healthcare providers on the current challenges and future directions of caring for WWE open-ended questions with appropriate prompts were used. The interview schedule was reviewed for relevance by 3 researchers and healthcare providers to establish face validity. A pilot test was conducted to ensure that the interview schedule can generate relevant qualitative data. All interviews were conducted by one female researcher (LZ) who was a student in the Master of Pharmacology program at An-Najah National University and a practicing pharmacist employed by the Palestinian Ministry of Health. The principal investigator (RS) who had experience in conducting qualitative interviews trained the researcher (LZ) to conduct the interviews. The researcher obtained informed consent from each interviewee. The interviewees were informed that the researchers had no conflicts of interest or intentions to influence their opinions/perspectives. All interviews were audio-recorded and field notes were taken. The contents of the interviews were transcribed verbatim. All recordings were audible and there was no need to repeat any of the interviews.

### 2.6 Data analysis

The transcripts were read multiple times to gain a general understanding of their contents. The interpretative description approach was used to qualitatively analyze the contents of the transcripts (80). This method was used because of its ability to enable identifying the main themes, subthemes, and patterns. The interpretative description approach was previously used in analyzing qualitative data that involved complex experiences in healthcare (47, 76, 81). In addition, the Leuven Qualitative Analysis Guide was also used to aid in identifying the main themes, subthemes, and patterns (82). Associations and similarities between the qualitative data points facilitated grouping these data into main themes, subthemes, and patterns.

## 2.7 Ethical considerations

The international ethical guidelines and the ethical principles of the Declaration of Helsinki were respected in this research. The study received approval from the Institutional Review Board (IRB) of An-Najah National University and the interviewees provided informed consents.

# Chapter Three

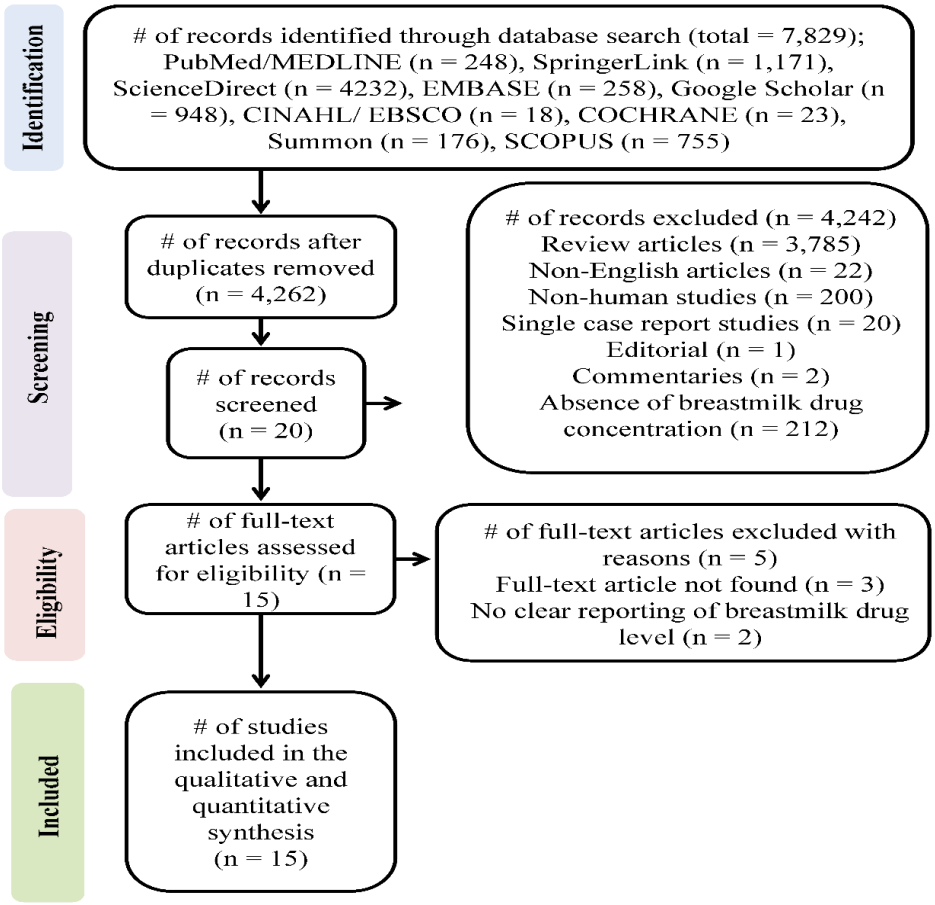
# Results

## 3.1 Results of the systematic review

In this systematic review, a total of 7,829 records were identified through the systematic search of the databases. When the duplicate records were removed, 4,262 records were screened against the eligibility criteria. A total of 15 records were included in this systematic review. Results of the search in the databases are presented in Figure 3.1. The summary of the included studies is shown in Table I.1 in Appendix I. Additional summaries of the articles included are provided in Appendix E.

**Figure 3.1**

*PRISMA flow diagram of the selection process*



### 3.1.1 Quality appraisal of the studies included

In general, the 15 studies included in this review were of acceptable quality. Subjects and settings were described, confounding factors were identified, and outcomes were measured validly and reliably in the 9 (100%) cross-sectional studies. On the other hand, the inclusion criteria were reported in 7 (77.8%) studies, the exposure was measured validly and reliably in 8 (88.9%) studies, objective and standard criteria were used for measurement of the condition in 5 (55.6%) studies, and appropriate statistical analysis was used in 5 (55.6%) studies. Strategies to deal with the confounding factors were not stated in any of the 9 (0%) studies. The quality appraisals of the 9 cross-sectional studies are shown in Appendix F. Of the 4 cohort studies, exposure was measured validly and reliably, confounding factors were identified, outcomes were measured validly and reliably, the follow-up time was sufficient to be long enough for the outcome to occur, and appropriate statistical analysis was used in the 4 (100%) studies. On the other hand, the participants were free from the exposure at the start of 2 (50%) studies, and follow-up was complete/reasons for loss of follow-up were described in 1 (25%) study. None of the studies (0%) reported selection of groups from similar populations, had similar exposure assigned to exposed and unexposed groups, reported strategies to deal with confounding factors, and utilized strategies to address in complete follow-up. The quality appraisals of the 4 cohort studies are shown in Appendix G. Clear criteria for inclusion were reported, the condition was measured in a standard and reliable way for all participants, valid methods were used for identification of the condition for all participants, clinical variables of the participants were reported, and outcomes or follow up results of cases were reported in the 2 (100%) case series studies. One of the case series studies (50%) had consecutive inclusion of the participants and one (50%) had completed inclusion of participants. Both case-series studies did not report the demographics of the participants, did not describe the site(s)/clinic(s), and did not use appropriate statistical analysis. The quality appraisals of the 2 case series studies are shown in Appendix H.

### 3.1.2 Characteristics of the studies included

#### 3.1.2.1 Study design

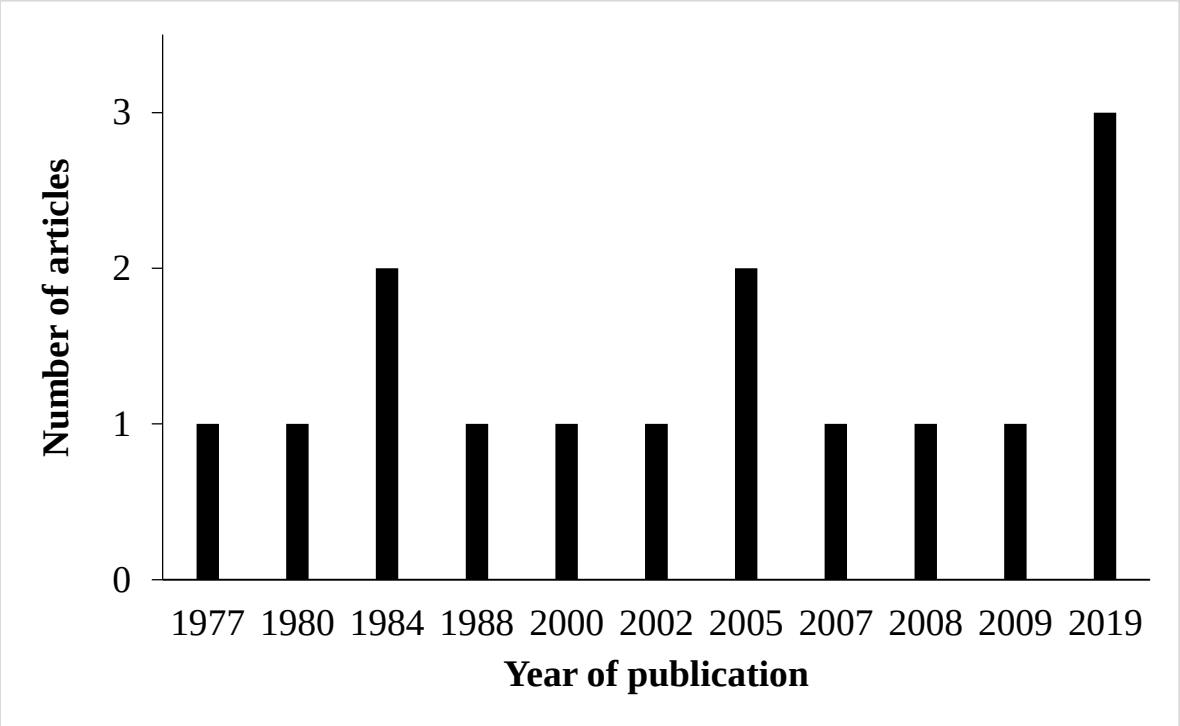
Of the studies included, 9 (60.0%) were cross-sectional studies (27, 28, 30, 32, 51-53, 83, 84), 4 (26.7%) were prospective cohort studies (33, 55, 85, 86), and 2 (13.3%) were case series studies (31, 54).

#### 3.1.2.2 Year of publication

The studies included in this review were published in the period between 1977 to 2019. The majority of the studies (66.7%) were published in the year 2000 and beyond. The year-wise publication trend is shown in Figure 3.2.

**Figure 3.2**

*Number of publications per year*

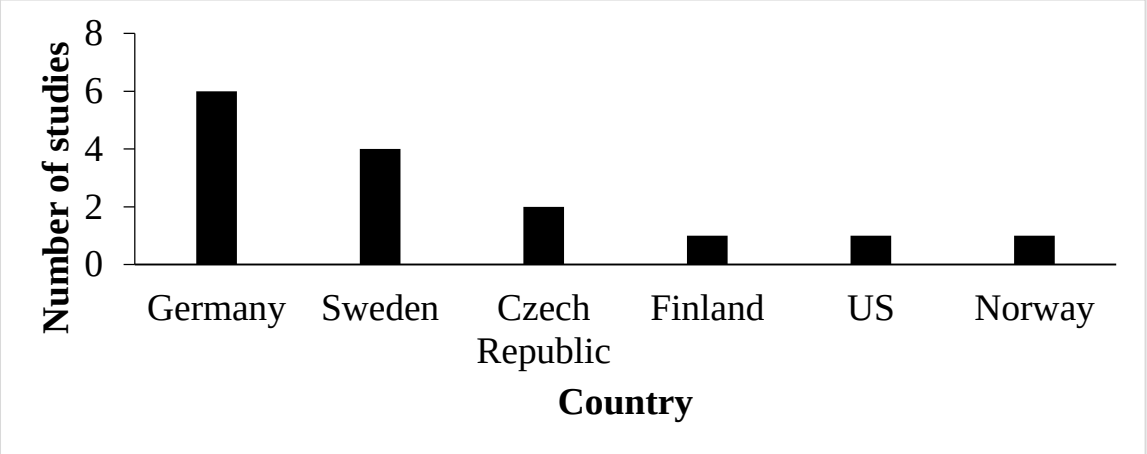



#### 3.1.2.3 Country of origin

Of the studies included in this review, the majority (66.7%) originated from Germany and Sweden. The rest of the studies originated from the US, Czech Republic, Finland, and Norway. The number of studies and their countries of origin are shown in Figure 3.3.

**Figure 3.3**

*Country of origin*




### 3.1.3 Characteristics of the women who donated the samples

The sample size in the included studies ranged from 5 to 43 WWE. The age of the WWE who donated samples ranged from 16 to 43 years old. It is noteworthy mentioning that the age of the WWE was not reported in 3 (20%) studies (51, 52, 83). The type of epilepsy and seizures were reported in 7 (46.7%) studies (28, 30, 32, 52, 53, 55, 85). In Paulzen et al.'s study, WWE had localization-related idiopathic epilepsy, epileptic syndromes with seizures of localized onset, and one had major depressive disorder (28). In Pynnonen et al.'s study, 2 WWE had psychomotor epilepsy and one had grand-mal epilepsy (55). In Kuhnz et al.'s study, all WWE had epilepsy with primary generalized seizures (52). In Ohman et al.'s study, WWE had generalized, partial, and seizures of undetermined type (32). In another study conducted by Ohman et al., WWE had idiopathic generalized epilepsy, localization-related epilepsy, and seizures of undetermined type (53). In Newport et al.'s study, lamotrigine was reportedly used for epilepsy and bipolar disorder (30). In Fotopoulou et al.'s study, WWE had frontal lobe seizures that progressed to a generalized convulsive (grand-mal) seizures, cryptogenic temporal lobe epilepsy that progressed to secondary generalized seizures, grand-mal seizures on waking up, absence seizures, and idiopathic juvenile myoclonic epilepsy (85). The characteristics of the WWE in the included studies are provided in Table 1.

### 3.1.4 The antiepileptic drugs quantified

The included studies reported concentrations of 8 AEDs in the breastmilk of WWE. Carbamazepine was quantified in 2 (13.3%) studies (55, 86), lamotrigine was quantified in 5 (33.3%) studies (27, 28, 30, 53, 85), primidone and its metabolites were quantified in 2 (13.3%) studies (51, 83) levetiracetam was quantified in 2 (13.3%) studies (31, 33), ethosuximide was quantified in 1 (6.7%) study (52), topiramate was quantified in 1 (6.7%) study (32), gabapentin was quantified in 1 (6.7%) study (54), and valproic acid was quantified in 1 (6.7%) study (84).

### 3.1.5 Doses of the antiepileptic drugs in the included studies

WWE in the majority of the studies received multiple AEDs rather than monotherapy with a single AED. Doses of the AEDs were not the same in the studies included in this review. Some studies included WWE who received variable doses of AEDs. Moreover, the samples were not collected at the same periods. Therefore, conducting a meta-analysis was not possible.

### 3.1.6 Analytical methods used to quantify concentrations of antiepileptic drugs

Different analytical techniques including high-performance liquid chromatography (HPLC), fluorescence polarization immunoassay (FPIA), reversed-phase HPLC, gas-liquid chromatography, chromatography-mass spectrometry, isocratic reversed-phase HPLC (RP-HPLC), liquid chromatographic-mass spectrometry (LC-MS), isocratic liquid chromatography, and gas chromatography were used to quantify concentrations of the AEDs in the different studies included in this review. HPLC was the most commonly used method to quantify AEDs.

#### 3.1.6.1 Breastmilk and blood concentrations of antiepileptic drugs

Concentrations of AEDs in breastmilk, maternal plasma, maternal serum, infant plasma, and infant serum are shown in Table 2. Additionally, breastmilk/maternal plasma, breastmilk/maternal serum, infant/maternal plasma, infant/maternal serum, infant plasma/breastmilk, and infant serum/breastmilk ratios are also shown in Table I.2 in Appendix I.

### 3.1.6.2 Risk assessment on breastfed infants

The theoretical doses calculated as EDI of AEDs and RID based on the breastmilk concentrations reported in the studies included in this review are shown in Table 3.1.

**Table 3.1**

*Estimated daily intake and relative infant dose of the antiepileptic drugs*

| | EDI (µg/g body weight/day) | | | |
|---|---|---|---|---|
| Antiepileptic drug/metabolite | Mean | SD | Relative infant dose (RID or %RID) | Reference |
| Carbamazepine | 0.43 | 0.007 | 2.72 | Froescher et al. (1984) |
| Carbamazepine | 0.28 | 0.004 | 3.70 | Pynnonen et al. (1977) |
| Carbamazepine epoxide | 0.26 | 0.004 | 1.63 | Froescher et al. (1984) |
| Carbamazepine epoxide | 0.13 | 0.002 | 2.26 | Pynnonen et al. (1977) |
| Lamotrigine | 0.47 | 0.007 | 3.83 | Paulzen et al. (2019) |
| Lamotrigine | 0.90 | 0.014 | 8.84 | Fotopoulou et al. (2009) |
| Lamotrigine | 0.59 | 0.009 | 9.18 | Newport et al. (2008) |
| Lamotrigine with inducer | 0.14 | 0.002 | 36.33 | Kacirova et al. (2019a) |
| Lamotrigine with valproic acid | 0.94 | 0.015 | 33.76 | Kacirova et al. (2019a) |
| Lamotrigine with neutral | 0.49 | 0.008 | 35.52 | Kacirova et al. (2019a) |
| Primidone | 0.72 | 0.011 | 4.96 | Nau et al. (1980) |
| Phenobarbital | 0.50 | 0.008 | 3.15 | Nau et al. (1980) |
| Phenylethylmalondiamide (PEMA) | 0.34 | 0.005 | 1.69 | Nau et al. (1980) |
| Gabapentin | 0.79 | 0.012 | 4.37 | Ohman et al. (2005) |
| Valproic acid | 278.16 | 4.318 | 1.90 | Kacirova et al. (2019b) |
| Ethosuximide | 8.61 | 0.134 | 31.49 | Kuhnz et al. (1984) |
| Levetiracetam | range: 0.83 – 4.52 | | 7.80 | Johannessen et al. (2005) |
| Levetiracetam | range: 1.0 – 6.21 | | 12.50 | Tomson et al. (2007) |
| Topiramate | range: 0.1 – 0.81 | | 12.18 | Ohman et al. (2002) |

SD: Standard deviation, RID: Relative infant dose

The calculated RID values were less than 10% for the majority of the AEDs. On the other hand, lamotrigine (27), ethosuximide (52), levetiracetam (6), and topiramate had RID values of more than 10% (32). The molecular descriptors, physiochemical, and pharmacological/ pharmacokinetic properties of the AEDs are shown in Table 3.2.

**Table 3.2**

*The molecular descriptors, physiochemical, and pharmacological/pharmacokinetic properties of the antiepileptic drug*[a]

| Antiseizure medication | Molecular mass (g/mol) | Polar Surface Area (Å$^2$)[b] | LogP[b] | Rule of Five[b] | Oral bioavailability | Human intestinal absorption | Ability to cross the blood brain barrier | Protein binding | Volume of distribution | Elimination half-life | pKa (Strongest Acidic)[b] | pKa (Strongest Basic)[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carbamazepine | 236.27 | 46.33 | 2.77 | Yes | 75% to 85% | High | + | 75 to 80% | 0.7 to 1.4 L/kg | 27 to 36.8 h | 15.96 | -3.8 |
| Primidone | 218.25 | 58.2 | 1.12 | Yes | 80% | High | + | 10.78 to 13.70% | 0.5 to 0.8 L/kg | 7 to 22 h | 11.5 | -6.2 |
| Phenobarbital | 232.24 | 75.27 | 1.41 | Yes | 95% | High | + | 20 to 45% | 0.61 L/kg | 53 to 118 h | 7.14 | - |
| Ethosuximide | 141.17 | 46.17 | 0.55 | Yes | 93% | High | + | 21.80% | 0.65 L/kg | 53 h | 10.73 | -6.6 |
| Lamotrigine | 256.09 | 90.71 | 1.93 | Yes | 98% | High | + | 55% | 0.9 to 1.3 L/kg | 14 to 59 h | 14.98 | 5.87 |
| Topiramate | 339.36 | 115.54 | 0.13 | Yes | 80% | High | + | 9 to 17% | 0.6 to 0.8 L/kg | 19 to 23 h | 11.09 | -3.7 |
| Gabapentin | 171.24 | 63.32 | -1.3 | Yes | 60% | High | + | < 3% | 58 ± 6 L | 5 to 7 h | 4.63 | 9.91 |
| Levetiracetam | 170.21 | 63.4 | -0.59 | Yes | 100% | High | + | < 10% | 0.5 to 0.7 L/kg | 6 to 8 h | 16.09 | -1.6 |
| Valproic acid | 144.21 | 37.3 | 2.8 | Yes | 90% | High | + | 18.50% | 11 L/1.73m | 13 to 19 h | 5.14 | -1 |

[a]The molecular descriptors, physiochemical, and pharmacological/pharmacokinetic properties were compiled from DrugBank (67)

[b]Predicted by ChemAxon (Cheminformatics, Budapest, Hungary).

The AEDs met Lipinski's rule of 5 (did not have more than 5 hydrogen bond donors, did not have more than 10 hydrogen bond acceptors, had a small molecular mass (< 500 Dalton), and had a logP of < 5), had relatively small polar surface area, had adequate oral bioavailability, and were able to cross the blood-brain barrier.

Exposure to AEDs via the breastmilk did not cause clinically significant adverse effects for the majority of the breastfed infants. In Pynnonen et al.'s study, no adverse effects were reported among the infants whose mothers were on carbamazepine therapy (55). However, Froescher et al. reported that only 1 of the 15 breast-fed infants whose mothers were on carbamazepine monotherapy had impaired suckling (86). Newport et al. reported no adverse effects among infants whose mothers were treated with lamotrigine (30). In their study, no breastfed infants developed a rash or showed symptoms of Stevens-Johnson Syndrome. Similarly, Ohman et al. reported that infants whose mothers were on lamotrigine therapy had no negative side effects (53). Kacirova et al., Fotopoulou et al., and Paulzen et al. did not report the risks of exposure to lamotrigine and valproic acid on the breastfed infants in their studies (27, 28, 84, 85). On the other hand, elevated platelet counts (mean: 520.5 [range: 329.0 – 652.0]) were observed in 7 of 8 infants with no clinically significant implications (30). Nau et al. reported that 8 of the newborns of the women who were on primidone and its metabolites were alert and had no feeding difficulties (83). However, during the first 5 days, 6 children were sluggish, hypotonic, and sucking poorly. After being deeply sedated during the first days, two of those infants exhibited marked withdrawal symptoms such as jitteriness, tremor, unmotivated sobbing, and sleep pattern disturbance throughout the second and third weeks (83). Kuhnz, et al. reported that during the first 2 weeks of life, infants whose mothers were on phenobarbital or primidone displayed characteristic sedative signs, and some primidone-exposed infants experienced withdrawal symptoms (51). Johannessen et al. reported that infants who were exposed to levetiracetam had a mean birth weight of 3,650 g (range: 2,970 g – 4,220 g) and appeared healthy (31). Similarly, Tomson et al. reported that infants whose mothers were on levetiracetam had no documented side effects (33). Kuhnz et al. reported that WWE who received a combination of ethosuximide/primidone or ethosuximide/phenobarbital had infants with bilateral clefting and a hare-lip (52). Sedation, poor sucking, and sleepiness were reported among 4 infants and withdrawal symptoms were reported among 5 infants (52). In Ohman et al.'s study, WWE who were

on topiramate had uncomplicated deliveries and gave birth to healthy newborns (32). In another study, Ohman et al. reported that one of the WWE who received gabapentin had early birth at week 33 of pregnancy (54). Additionally, one infant experienced mild hypotonia and cyanosis 8 hours postnatal, but the infant was discharged from the hospital 4 days later in healthy status (54).

### 3.2 Results of the qualitative study

Interviews were conducted with 20 participants. The total duration of the interview time was 745 min (12.4 h). The median interview duration was 36 (30, 40) min. Of the participants, 6 (30.0%) were neurologists, 5 (25%) were gynecologists, 3 (15%) were psychiatrists, 1 (5%) was internist, and 5 (25%) were clinical pharmacists. Of all interviewees, 6 (30%) were female, 13 (65%) were 40 years and older, and 9 (45%) had a practice experience of 20 or more years. The majority (60%) of the interviewees interacted with more than 2 WWE per month. The participants received training in Palestine and elsewhere. Of the participants, 5 (25%) received training in Jordan, 2 (10%) received training in Egypt, 2 (10%) received training in Romania. Other interviewees received training in the UK, Germany, Italy, Turkey, Ukraine, Russia, Tunisia, and Algeria. The participants worked in governmental hospitals, private hospitals, and clinics of the UNRWA. The detailed characteristics of the participants are shown in Table 3.3.

**Table 3.3**

Characteristics of the participants (n = 20)

| Characteristic | n | % |
|---|---|---|
| Gender | | |
| Male | 14 | 70.0 |
| Female | 6 | 30.0 |
| Age (years) | | |
| < 40 | 7 | 35.0 |
| ≥ 40 | 13 | 65.0 |
| Academic degree/board certificate | | |
| MD/PhD | 15 | 75.0 |
| BSc/MSc | 5 | 25.0 |
| Specialty | | |
| Neurology | 6 | 30.0 |
| Obstetrics and gynecology | 5 | 25.0 |
| Psychiatry | 3 | 15.0 |
| Internal medicine | 1 | 5.0 |
| Clinical pharmacy | 5 | 25.0 |
| Number of years in practice | | |
| < 20 | 11 | 55.0 |
| ≥ 20 | 9 | 45.0 |
| Number of WWE seen per month | | |
| 1-2 | 8 | 40.0 |
| ≥ 2 | 12 | 60.0 |

BSc: Bachelor of Science, MD: Doctor of Medicine, MSc: Master of Science, PhD: Doctor of Philosophy, WWE: WWE

### 3.2.1 Major themes, subthemes, and patterns that emerged from the qualitative analysis

The qualitative data collected and analyzed in this study led to the emergence of the following major themes:

#### 3.2.1.1 Diagnosis and care for patients with epilepsy

##### 3.2.1.1.1 Diagnosis of patients with epilepsy in Palestine

In Palestine, patients with epilepsy including WWE are diagnosed after being examined by a neurologist in governmental hospitals, private hospitals, and neurology clinics. The participants stated that the history of the patient would be taken, a physical examination would be performed by a neurologist, and laboratory and medical imaging tests would be ordered. These would include complete blood count (CBC), electrolytes, creatine

kinase (CK), prolactin, lumbar puncture, electroencephalogram (EEG), magnetic resonance image (MRI), and computerized tomography (CT) scan. One of the neurologists stated:

"…we would ask the patient or someone who has witnessed the seizure to describe what has happened to the patient. We would request an EEG, an MRI, and a CT scan." A female neurologist with 8 years in practice

Another neurologist added:

"…somebody must have witnessed the patient and what the patient had suffered. We might witness that the patient has bitten their tongue, urinated, or has broken some limb. We would then request an EEG, MRI, and we should request a blood test to see if prolactin, CK, and WBCs levels were high after the seizure." A male neurologist with 38 years in practice

The participants stated that they would follow a differential diagnostic approach to differentiate an epileptic seizure from a tantrum, a febrile seizure, or nonepileptic seizures due to other health conditions like hypoglycemia, meningitis, eclampsia, encephalitis, or migraine headaches.

The participants stated that the Palestinian practice lacked a formally adopted protocol/criteria used in guiding the diagnosis of patients with epilepsy. One of the neurologists stated:

"In Palestine, no specific protocol was formally adopted. Every neurologist follows the protocols adopted in their places of training. The majority of neurologists follow the European protocols." A female neurologist with 8 years in practice

#### 3.2.1.1.2 Caring for patients with epilepsy

Again, the participants recognized the lack of formally adopted protocols to guide caring for patients with epilepsy, notably WWE. The neurologists in this study stated that they would care for patients depending on the type of seizures. The participants stated that WWE would be referred to neurologists who would probably prescribe them AEDs. Lack of care services tailored to the needs of WWE was recognized by the participants. One of the participants stated:

“There are no care services tailored to the needs of WWE. Every WWE has to follow up with a neurologist she chooses to visit. Once appropriate AEDs are prescribed, WWE can collect their medications from the nearest primary healthcare center to their place of residence.” A male gynecologist with 20 years in practice

#### 3.2.1.2 General issues in caring for patients with epilepsy

##### 3.2.1.2.1 Lack of adherence to taking AEDs

The neurologists recognized the widespread lack of adherence to taking AEDs. One of the neurologists stated:

“Unfortunately, this could be attributed to the health literacy of the patient. Many patients with epilepsy deny having epilepsy. Some of the patients believe they are possessed by demons. Therefore, they visit spiritual healers. They are not convinced that this is a health condition that they have to adhere to taking their treatment to avoid experiencing seizures. The physician has always to explain to the patient that seizures are surplus electrical charges and adherence to taking medications would protect them from experiencing seizures in 70%-80% of the cases. When patients continue to experience seizures, they return to the physician angry.” A male neurologist with 10 years in practice

##### 3.2.1.2.2 Experiencing side effects

The participants recognized that AEDs are associated with clinically significant side effects. The participants stated that clinicians have to deal with these side effects when experienced by the patients. Patients have to receive the most appropriate AEDs that can control their seizures with minimal side effects. The participants also stated that the patients need to be informed of the long-term adverse effects of their medications and how to minimize them. One of the participants shared:

“All AEDs have side effects. In case the patient could tolerate these side effects, then they should adhere to taking their AEDs. Sometimes, patients might experience epidermolysis as they use carbamazepine. This could be serious and requires that we consider stopping taking the medication immediately and put the patient on another treatment. Side effects might be avoided by reducing the dose. For example, side effects are more likely at high doses of carbamazepine. The risk of side effects can be reduced

if we start the patient on carbamazepine and gradually increase the dose over 3-4 days. We can order a CBC to see if the WBC count decreases or not." A male psychiatrist with 39 years in practice

#### 3.2.1.2.3 Drug interactions

The participants stated that the treatment plan should consider the risks of drug interactions. One of the participants shared:

"The treatment plan should include the least possible number of drugs. We need to consider increasing the dose to the maximal daily dose before we think about adding another drug. Whenever another drug to be added to the treatment plan, the risk of drug interactions should be evaluated. Patients should be informed that they should not take any medications without consulting their physician." A male neurologist with 41 years in practice

#### 3.2.1.2.4 Periodic evaluation of the treatment plan

The neurologist stated that the treatment plan needs periodic evaluations. The physician might also order blood tests, liver function tests, and levels of certain electrolytes. One of the neurologists shared:

"…we have to evaluate the treatment plan. We could start with a monthly evaluation and when the patient is stabilized, we can for periodic evaluations every 3-6 months depending on the number of seizures experienced by the patient. We have to screen for partial as well as generalized seizures." A male neurologist with 10 years in practice

### 3.2.1.3 Consideration of women's issues in the pharmacotherapy of epilepsy

#### 3.2.1.3.1 Preconception consultations

The participants stressed on the importance of preconception consultations with WWE.

##### 3.2.1.3.1.1 Risk of teratogenicity and considering switching AEDs

The participants stated that they might consider switching AEDs before conception. One of the neurologists shared:

"…in case there was planning for conception, we need to consider switching AEDs months ahead of conception. We need at least 3 months." A male neurologist with 10 years in practice

"…in case the pregnancy was not planned, we might need to consider continuing the same AED, even if the patient was on valproic acid." A male neurologist with 12 years in practice

The neurologists stated that they would prefer to put the patient on monotherapy.

The participants stated that they would recommend WWE to take folic acid supplements 3 months before conception. Other gynecologists stated that they would also recommend WWE to take supplements of calcium and B vitamins.

"…I would recommend them to take folic acid, B vitamins, and calcium three months before conception." A gynecologist with 13 years in practice

Although the participants stated that the vast majority of WWE would deliver normal babies, the study participants recognized that some AEDs could be associated with a higher risk of teratogenicity. Among these, neural tube defects like spina bifida, lower intelligence quotient (IQ), autism, cleft palate, cardiac malformation, and other malformations.

One of the clinical pharmacists shared:

"…the risk of teratogenicity is higher by 2-5-fold when women are on AEDs." A female clinical pharmacist with 19 years in practice

Despite the risk of teratogenicity, the participants stressed on the importance of adhering to taking AEDs.

"…the risk of teratogenicity is not that high. The risk [of teratogenicity] depends on the type of epilepsy, the type of AEDs, and the dose. Valproic acid could be associated with higher risk compared to other drugs like lamotrigine." A male gynecologist with 9 years in practice

The participants recognized that some AEDs could be associated with a higher risk for teratogenicity and some AEDs could be safer to be used for WWE, notably, those of childbearing age.

"…valproic acid, phenytoin, and phenobarbital have a higher risk compared to lamotrigine and levetiracetam." A male neurologist with 38 years in practice

#### 3.2.1.3.1.2 Balancing benefits versus risks of taking AEDs

The participants stressed on balancing benefits against risks of using AEDs. One of the pharmacists shared:

"…we must evaluate the risks and the benefits of using AEDs during pregnancy. This would take into consideration the type of seizures, number of seizures before pregnancy. We would put the patient on the AED that has the lowest risk for teratogenicity. We also would consider using the lowest effective dose. In case the patient had not suffered any seizures in the past 2-5 years, we would consider stopping AEDs." A female clinical pharmacist with 19 years in practice

The participants stated that seizures would be riskier for the fetus than taking AEDs. One of the neurologists shared:

"Experiencing a seizure is riskier than taking AEDs because seizures could cause a reduction in the oxygen reaching the fetus and could be associated with miscarriage." A male neurologist with 12 years in practice

### 3.2.1.3.2 During pregnancy

The participants stressed on the importance of controlling seizures during pregnancy. One of the gynecologists stated:

"…frequency of seizures might decrease or increase during pregnancy. I would say the frequency of seizures might increase in about one-third of WWE. WWE who did not experience seizures in the past 9 months would more likely continue their pregnancy free from seizures in the vast majority of the cases." A gynecologist with 25 years in practice

Another gynecologist added:

"…we need to optimize control over seizures with AEDs because seizures can increase the risk of miscarriage, premature delivery, cesarian delivery, and postpartum hemorrhage." A gynecologist with 9 years in practice

The participants recognized the effects of pregnancy on AEDs. One of the clinical pharmacists shared:

"In pregnancy, some enzymes are induced and albumin levels decrease. This would affect the disposition of AEDs, especially, those with high plasma protein binding." A clinical pharmacist with 20 years in practice

The gynecologists stated that they would screen for fetal malformations using ultrasonographic methods like nuchal translucency/early anatomy ultrasound, maternal serum α-fetoprotein (MSAFP), estriol, and human chorionic gonadotropin (hCG). The participants stated that some other screening methods like fetal echocardiography might also be used to detect potential congenital malformations.

"…we would request a nuchal translucency/early anatomy ultrasound. We would also request some blood and amniotic fluid tests to screen for potential malformations." A female gynecologist with 5 years in practice

#### 3.2.1.3.3 Bone health

The participants recognized the importance of considering the bone health of WWE as AEDs can decrease bone density, osteoporosis, and seizures might cause bone fractures. One of the neurologists stated:

"I would give WWE calcium and vitamin D supplements. Now and then, I would request a dual-energy X-ray absorptiometry scan." A neurologist with 12 years in practice

The neurologists stated that newer AEDs are safer for bone health compared to older AEDs. One of the neurologists shared:

"Lamotrigine and levetiracetam are less likely to affect bone health." A neurologist with 10 years in practice

#### 3.2.1.3.4 Catamenial epilepsy

The gynecologists recognized the existence of catamenial epilepsy among WWE. One of the gynecologists shared:

"Some women experience intensities in seizures just before or during their mensural period." A female gynecologist with 5 years in practice

Concerning treatment, the neurologists stated that they would use topiramate, lamotrigine, and levetiracetam. They also stated that acetazolamide and lorazepam might be used as short-term during the menstrual period with intensities in seizures. One of the neurologists shared:

"…the patient might use lorazepam in the period when seizures intensify." A male neurologist with 10 years in practice

The gynecologists stated that hormonal therapies like progesterone and clomiphene might help manage catamenial epilepsy.

#### 3.2.1.3.5 Menopause and hormonal replacement therapy

When hormonal therapies are used to alleviate signs and symptoms of menopause, the frequency of seizures might change. The participants recognized the importance of considering using hormones that reduce the frequency of seizures and avoiding hormones that might increase the frequency of seizures.

"I would avoid all hormones replacement therapy in WWE." A gynecologist with 25 years in practice

#### 3.2.1.3.6 Effects of AEDs on contraceptives

The participants recognized the effects of AEDs on oral contraceptives, notably, topiramate, carbamazepine, phenytoin, clonazepam, and phenobarbital. On the other hand, the participants recognized that they can opt for AEDs with fewer effects on the metabolism of oral contraceptives like valproic acid, lamotrigine, levetiracetam, and gabapentin. One of the neurologists shared:

“AEDs interact with oral contraceptives and reduce their efficacy. Valproic acid, on the other hand, would not induce enzymes that are involved in the metabolism of oral contraceptives.” A male neurologist with 46 years in practice

The gynecologists stated that they would recommend using physical barriers like condoms and would opt to increase the doses of ethinylestradiol (at least 5 μg) in the contraceptive system used for WWE. One of the gynecologists shared:

“I would opt for intrauterine devices containing levonorgestrel or medroxyprogesterone injections for WWE.” A male gynecologist with 9 years in practice

The participants also expressed their concerns regarding increasing the dose of combined oral contraceptives as a source of higher risk for ischemia and thus higher risks for experiencing seizures. The participants also recognized that using combined contraceptives with lamotrigine might increase the frequency of seizures.

#### 3.2.1.3.7 Effects of epilepsy and AEDs on the menstrual cycle

During the menstrual cycle, the participants recognized the epileptogenic effects of estrogen and antiepileptic effects of progesterone. The participants recognized the potential effects of AEDs on the incidence of polycystic ovary syndrome, amenorrhea, hypothalamic fractional hyperprolactinemia, and hyperandrogenemia. These effects were said to be more pronounced with valproic acid and phenytoin.

“Estrogen and progesterone are endogenous female sex hormones. The brain is affected by the actions of these hormones. Estrogen can increase the chances of seizures, especially, in the period of ovulation. On the other hand, progesterone can decrease the chances of seizures.” A clinical pharmacist with 19 years in practice

#### 3.2.1.3.8 Eclamptic seizures

The participants stated that they would manage eclamptic seizures using intravenous or intramuscular magnesium sulfate. One of the gynecologists shared:

“I would opt for the treatment of choice by administering an intravenous infusion of magnesium sulfate (5 g) for 20 to 30 min and then 1-2 g hourly for 24 hours.” A male gynecologist with 13 years in practice

#### 3.2.1.3.9 Breastfeeding

Although AEDs are excreted in breastmilk, the participants stated that they would evaluate the risks and generally would recommend WWE to breastfeed their infants. On the other hand, the participants stressed on the importance of screening for potential adverse effects of AEDs. One of the neurologists shared:

"AEDs might be associated with serious adverse effects like Steven Johnson Syndrome." A male neurologist with 10 years in practice

Another female neurologist with 8 years in practice shared:

"I would prefer to use lamotrigine, oxcarbazepine, topiramate, levetiracetam for breastfeeding WWE. Mothers should pay attention if the baby showed any signs of sedation, sluggishness, or laziness."

#### 3.2.1.3.10 Sexual activity

The participants stated that some AEDs like phenytoin and carbamazepine decrease libido and impacted the sexual life of WWE. One of the gynecologists shared:

"AEDs, especially enzyme inducers, decrease arousal and libido among WWE. Some epilepsies are associated with decreased blood flow to the genitals, which in turn, would decrease stimulation. Additionally, some AEDs cause dryness of the vaginal fluids, thus might negatively impact the sexual life of WWE." A male gynecologist with 9 years in practice

The participants stated they would counsel WWE on the importance of adherence to taking their AEDs, controlling their seizures, using lubricants, and might opt to refer WWE to psychosocial support.

### 3.2.2 Current challenges in caring for WWE

The current challenges in caring for WWE in Palestine were grouped under healthcare system-related, healthcare provider-related, patient-related, and society-related challenges.

#### 3.2.2.1 Challenges related to the healthcare system

The interviewees stated that there was a lack of easily available, accessible, and affordable neurology services. Therefore, patients might need to travel from one place to another while seeking diagnostic, treatment, and/or care services. One of the female interviewees shared:

"… not all major healthcare centers in the country offer neurology services. Therefore, patients often need to travel to another city to receive adequate neurology care."

Another challenge was the lack of services tailored to the needs of WWE. The participants stated that there was a need for specialized care centers that would cater to the needs of WWE. One of the female neurologists shared:

"We need to see highly specialized care centers offering services to WWE. These centers would be expected to offer neurology, obstetrics and gynecology services. One would expect these centers to be well-equipped with the needed tools to screen for fetal malformations."

The lack of female neurologists was another challenge highlighted by the interviewees. One of the male interviewees shared:

"WWE would feel more comfortable dealing with female healthcare providers including neurologists."

The last challenge highlighted by the interviewees was the lack of availability, accessibility, and affordability of new, safe, and effective AEDs. One of the female interviewees shared:

"…not all AEDs are provided free of charge by governmental dispensaries. Some new AEDs are expensive and beyond the reach of many WWE."

#### 3.2.2.2 Challenges related to the healthcare providers

The interviewees recognized that some healthcare providers lack understanding of the nature of epilepsy, seizures, and/or women's issues in epilepsy. Because of the nature of the disease, WWE are often subjected to stigma and discrimination. One of the male interviewees shared:

“Women in our society are deprived of many rights. WWE often lack attention to their health issues.”

The interviewees also stressed on the importance of follow-up visits and the absence of patient outreach systems. One of the interviewees shared:

“Many healthcare providers do not establish an effective relationship with the patients. Therefore, many WWE miss on their regular follow-up visits.”

The interviewees also recognized the need for encouraging elaborative discussion of women’s health issues with WWE. One of the participants shared:

“There should be an elaborative discussion when WWE plan for getting married, issues related to conception and pregnancy, breastfeeding, and social life issues. Because women in the society have to take care of the house work, WWE are especially vulnerable to accidents.”

#### 3.2.2.3 Challenges related to the patients

The interviewees stated that some WWE lack awareness and understanding of their disease. Therefore, they might deny having the disease or attempt to hide it from the spouse, family, friends, and/or the society. One of the interviewees shared:

“Many WWE are ignorant of the nature of their disease or seizures. Therefore, they would deny it or attempt to hide it. Some would attempt to explain it as a possession by demons, witchcraft, or waves of tantrums. Later, they would realize that it is a manageable disease.”

The interviewees were aware that some WWE would avoid seeing diagnosis or healthcare. Additionally, many WWE would not adhere to taking their AEDs. One of the interviewees shared:

“WWE might not take their AEDs to avoid being embarrassed. They would prefer to deny or hide their disease.”

Another interviewee added:

“Many WWE would hide their disease from their spouses, relatives, friends, and neighbors. They might avoid taking AEDs in front of anybody.”

Another interviewee added:

“WWE might not know how, when, and at what frequency they should take their AEDs because the patient herself did not visit the doctor, but her mother did on her behalf.”

The interviewees also stated that some WWE do not follow up with their healthcare providers and/or would not disclose their health conditions to their healthcare providers. Therefore, they might end up experiencing drug-drug interactions or being prescribed a contraindicated drug. One of the interviewees shared:

“People lack awareness about the nature of the disease. By fear of stigma and discrimination, WWE often attempt to stop taking their AEDs without medical advice, especially, when the frequency of their seizures decreases.”

Another interviewee added:

“WWE would even feel embarrassed to discuss their very intimate problems like their sexual life.”

#### 3.2.2.4 Challenges related to the society

The interviewees stated that a lack of awareness and understanding of the nature of epilepsy and seizures were highly prevalent in society at large. As a result, patients with epilepsy, notably WWE are subjects to stigma and discrimination. One of the interviewees shared:

“Patients with epilepsy are subjects to stigma in our society. It is even worse for WWE who would experience discrimination in their social life, family life, and work.”

Another interviewee added:

“WWE are often overwhelmed by the stigma and discrimination they experience from the society. Many WWE would fear receiving a diagnosis or seeking care.”

The participants stressed on the importance of addressing the lack of acceptance of patients with epilepsy in society. One of the participants shared:

“Acceptance by the society is one of the main issues for patients with epilepsy, especially WWE. You can feel it when parents would tell you that their daughter has

epilepsy and she is about to get engaged or married. Would her fiancé or his family accept her even though her seizures were controlled?"

Another interviewee shared:

"…. our society does not accept them [patients with epilepsy], they are being treated as mentally handicapped. This would add salt to their injury."

### 3.2.3 Future directions in caring for WWE

Similar to the challenges, the future directions in caring for WWE in Palestine were grouped under healthcare system-related, healthcare provider-related, patient-related, and society-related directions.

#### 3.2.3.1 Directions related to the healthcare system

The interviewees stressed on the importance of awareness campaigns to increase awareness of healthcare providers within the healthcare system on the availability of new generations and safe AEDs that can be used for WWE of childbearing age. One of the interviewees shared:

"Today, new generations of safe AEDs are increasingly available. WWE can take some of these AEDs safely during pregnancy without jeopardizing the integrity and health of their fetus. Some AEDs are safe during breastfeeding."

The interviewees also recognized that there was a need to improve the availability/accessibility/affordability of neurology services in all regions because some WWE needed to travel to seek healthcare. One of the interviewees shared:

"Currently we are short with neurologists. We need to encourage future physicians to choose neurology as a specialty."

Another interviewee shared:

"In every region, there should be a neurologist to follow up with patients with epilepsy. Periodic visits should be scheduled and appropriate counseling should be provided to WWE. Pregnant WWE should be counseled on the importance of prenatal screening to detect fetal malformations."

The interviewees stressed on the need for the establishment of healthcare centers that would cater to the needs of WWE. One of the interviewees shared:

“We need to establish a center equipped with the necessary tools to provide tailored neurology, obstetrics and gynecology services for WWE.”

The participants also stressed on encouraging female physicians to specialize in neurology because the healthcare system is short with female neurologists. One of the interviewees shared:

“There are many women’s issues in epilepsy that WWE would feel more comfortable sharing with a female neurologist. Today, WWE might share these issues with female nurses. Although nurses might discuss these issues with their fellow healthcare providers like neurologists, still, female neurologists would be expected to be more competent in addressing these health issues.”

The participants highlighted the importance of increasing availability/accessibility to new, safe, and effective oral AEDs. One of the interviewees shared:

“We need to increase access to the new and safe AEDs. These AEDs were shown to be safe to be used in WWE of childbearing age.”

The participants also stressed on the importance of establishing policies to eliminate stigma and discrimination against patients with epilepsy, especially against women.

#### 3.2.3.2 Future directions related to the healthcare providers

The participants stressed on the importance of increasing awareness and knowledge of healthcare providers concerning epilepsy and women’s issues in epilepsy. One of the participants shared:

“Healthcare providers who interact with WWE should be targeted with awareness campaigns as well. They [healthcare providers] need to be knowledgeable of epilepsy, seizures, and how seizures are managed in women.”

The interviewees also stated that there was a need to establish a patient outreach system to remind the patients of their follow-up visits. One of the participants shared:

“There should be an outreach system to remind the patients with their follow-up visits.”

The participants stated that neurologists should formally adopt protocols/criteria for the diagnosis and caring for WWE. One of the interviewees shared:

“Professional bodies should adopt protocols, guidelines, and policies that guide the diagnosis and care of WWE.”

The participants stated that these protocols, guidelines, and policies might allow personalizing the treatment plans for the needs of each WWE. Additionally, the participants stressed on the importance of elaboratively discussing women’s health issues during the clinical encounter with WWE.

#### 3.2.3.3 Future directions related to the patients

The participants stated that WWE should seek and receive education about their disease and treatment. WWE should be encouraged to schedule periodic follow-up visits with their healthcare professionals. One of the interviewees shared:

“Awareness campaigns should target WWE themselves to understand their disease and how to cope with it and with the treatment. WWE should be educated on how they can proceed with their daily life.”

Another interviewee added:

“WWE should be educated that the majority of the patients would achieve control over their seizures using AEDs.”

The participants also stressed on the importance of encouraging WWE to seek healthcare. One of the interviewees shared:

“WWE often receive their AEDs from the dispensaries of the ministry of health. These could be opportunities to meet with the patients, listen to them, and educate them how to cope with their disease and make the best out of their treatment.”

The participants also stressed on the importance of educating WWE on the factors that could precipitate seizures like using stimulants, electronic games, lack of enough sleep, some drugs, and some foods.

The participants stressed on the importance of addressing the lack of adherence to taking AEDs. One of the participants shared:

“Many WWE stop taking their AEDs against medical advice. WWE should be counseled not to do that.”

WWE should be encouraged to disclose and discuss their health issues with their caring healthcare professionals.

#### 3.2.3.4 Future directions related to the society

The participants stated that the society at large should be targeted with awareness campaigns that would increase the acceptance of the patients and their inclusion in society. One of the participants shared:

“We need to increase awareness of the society about epilepsy and patients with epilepsy. People should understand that epilepsy is not a mental illness and they [people] should refrain from thinking that patients with epilepsy are insane or have a mental handicap.”

Another interviewee added:

“There should be campaigns to improve acceptance and inclusion of patients with epilepsy in the society. People should understand that patients with epilepsy can get married, have children, do housework, and have nothing wrong with their mental capacity. They have nothing to be ashamed or embarrassed about.”

# Chapter Four

# Discussions and Conclusions

## 4.1 Discussion of the systematic review

International health organizations recommend exclusive breastfeeding of newborn infants for the first six months of their life. According to recent position papers, these recommendations also apply to WWE who received AEDs (6, 12-15). Breastmilk concentration, EDIs, and RIDs of AEDs were not systematically reviewed before. In this review, concentrations of AEDs in breastmilk of lactating WWE were reviewed, theoretical doses as EDIs and RIDs were estimated, and risks to infants as a result of exposure to AEDs from breastmilk were summarized. Findings of this systematic review can be used by clinicians, breastfeeding counselors, midwives, nurses, and other healthcare providers to inform decisions/recommendations relevant to breastfeeding for WWE.

In this review, 15 studies were included. This small number of studies might highlight the paucity of information on the concentrations of AEDs in breastmilk of lactating WWE. The findings of this systematic review might present a call for more research in this area. It is noteworthy mentioning that historically pregnant and lactating women were excluded from clinical studies due to safety, ethical, and legal concerns (87). Recently, regulatory authorities have encouraged the inclusion of pregnant and lactating women in clinical studies, especially those affected by the condition/disease to be treated (87-89). This change in position aimed to improve the healthcare of those women. In this review, the majority of the studies included were published beyond the year 2000.

Cross-sectional and cohort studies lacked strategies to deal with confounding factors. This should have limited conducting a meta-analysis to pool concentrations of AEDs from the different studies (90). Additionally, cohort studies were needed to improve the selection of the subjects in the exposed and unexposed groups and follow-up of the participants. The case-control studies needed to report the demographics of the participants, study settings/sites, and use appropriate statistical methods. These findings might be a call for researchers to address these quality issues in future studies.

All studies included in this review originated from developed countries. The findings of this study indicate a need for assessing AEDs in lactating WWE and the risks of infant exposure in developing countries. Recently, there have been many calls to encourage the inclusion of participants, including women, from developing countries in global clinical studies (91-93). The sample sizes of the included studies were relatively small. Although this could be explained, at least in part, by the difficulty of obtaining breastmilk samples from WWE, however, planning for future studies should consider obtaining more samples from WWE at more frequent time points (94-96). This would produce more reliable findings. Planning should also consider the inclusion of WWE who received similar AEDs at similar doses. Additionally, the inclusion of patients with a similar type of epilepsy would allow more meaningful comparisons.

In this review, large variability in the AEDs, doses, and sample collection times were observed. In addition to sampling, large variabilities were observed in terms of sample preparation and the analytical methods used to quantify the levels of AEDs. It is noteworthy mentioning that the limits of detection and quantification can differ significantly between methods. These variabilities should be considered when interpreting the findings of the studies included (97, 98). Quantifying levels of AEDs using the same methods would allow comparing results from different studies.

In the studies included, levels of lamotrigine, levetiracetam, carbamazepine, primidone/ phenobarbital, ethosuximide, topiramate, gabapentin, and valproic acid were reported. Lamotrigine, levetiracetam, carbamazepine, and topiramate are the most commonly prescribed AEDs for WWE of childbearing age (99, 100). In this review, lamotrigine was quantified in 5 studies (27, 28, 30, 53, 85), levetiracetam was quantified in 2 studies (31, 33), carbamazepine was quantified in 2 studies (55, 86), and topiramate was quantified in 1 study (32). The large variability in the AEDs used in the included studies could be explained by the variability in the type of seizures experienced by the WWE included in these studies.

Detectable concentrations of AEDs were reported in plasma or serum samples of the infants after exposure via breastmilk. Additionally, some EDIs and RIDs of AEDs were high. These findings were not surprising because the majority of the AEDs are relatively small molecules with adequate lipophilicity that enable them to cross biological membranes including the blood-brain barrier. The studies included in this

review have shown that many AEDs were excreted into breastmilk in high concentrations. However, the majority of these AEDs did not produce significant adverse effects that warrant discontinuation of breastfeeding. Lamotrigine, levetiracetam, carbamazepine, topiramate, valproic acid, and gabapentin were not associated with clinically significant side effects among the breastfed infants in the studies included in this review (27, 28, 30-33, 53, 55, 85, 86). These AEDs did not seem to retard growth, development, intelligent quotient (IQ), and verbal abilities of the breastfed infants (99-101). However, infants exposed to these AEDs via breastmilk might be monitored for signs of poor suckling/inadequate weight gain, sedation/ drowsiness/ irritability, impaired liver function, abnormal blood cell/platelet count, and developmental milestones (101). Moreover, exposure to lamotrigine warrants monitoring for apnea and rashes.

Infants who were exposed to primidone and its metabolites (phenobarbital and phenylethylmalonic acid) from breastmilk were sluggish, hypotonic, sucking poorly, and after being sedated, the infants experienced withdrawal symptoms (51, 83). These reported effects were consistent with the mechanism of action and adverse effects profile of primidone and its metabolites (51, 52, 83, 102). It has been recommended that breastfeeding might be limited or discontinued in case of excessive sedation/drowsiness and/or poor weight gain (101). More serious adverse effects and even malformations including bilateral clefting and a hare-lip were reported among the infants who were exposed to combinations like ethosuximide/primidone or ethosuximide/phenobarbital (52). Those infants experienced intrauterine exposure to these AEDs with known teratogenic potential (103).

### 4.1.1 Strengths and limitations of the study

The findings of this study might be interpreted considering many strength points. First, the protocol of this systematic review was registered in the most popularly used registry for systematic reviews. Additionally, a preliminary search was conducted in international databases to check for current and/or underway systematic reviews on the topic. Registering the protocol of a systematic review in an international searchable registry a priori and conducting preliminary searches would allow avoiding/minimizing the number of duplicate reviews. Second, this systematic review was conducted and reported using the PRISMA checklist. Adherence to the PRISMA checklist should have

allowed transparent reporting of the methods and findings of this review. Third, the search strategy was informed by the population/problem, intervention, comparison, outcome, and study design (PICOS) strategy. The use of this strategy was shown to refine the search, reduce false positives, and improve the identification of relevant documents. Fourth, the search was conducted in 10 international databases. Together, these large international databases should have allowed the identification of all relevant documents. The additional search of the gray literature was another point of strength. Fifth, the quality of the selected studies was appraised using the checklist that was validated and adopted by a well-known institution. Finally, all steps in this review were conducted by 2 researchers who had experience in conducting systematic reviews.

On the other hand, this systematic review had some limitations. First, the search results were filtered for those published in the English language only. This step might have eliminated important documents that might have been published in other languages. Second, the findings of this study were synthesized qualitatively. Although qualitative synthesis could be interesting, a meta-analysis would be more interesting. However, due to the heterogeneity of the findings, large variability of doses, sampling, and analytical methods, a meta-analysis was not conducted. Third, the selection of studies that reported concentrations of AEDs might have resulted in the exclusion of some important studies that could have reported more adverse effects of the AEDs in breastfed infants. Finally, follow-up was a major limitation in the studies included in this review. Findings could have been more meaningful if longitudinal studies that followed up infants exposed to AEDs via breastmilk for a long time.

## 4.2 Discussion of the qualitative study

### 4.2.1 Summary of the main findings of the study

Recently, there have been many calls to improve and benchmark healthcare delivery in many healthcare systems around the world (20, 56, 57). This qualitative explorative study explored the perspectives of neurologists, gynecologists, clinical pharmacists, psychiatrists, and internists on the current status, key challenges, and future directions in caring for WWE. The challenges and future directions were healthcare system-, healthcare provider-, patient-, and society-related. The findings of this study could be informative to decision-makers in the healthcare authorities, professional groups, and

patient advocacy groups who could be interested in improving the care of WWE in Palestine and in similar healthcare systems.

### 4.2.2 Appraisal of the methods used in this study

In this study, an explorative qualitative approach was used. Qualitative approaches are powerful in exploring perspectives of stakeholders on a certain issue, notably, in healthcare (47, 76, 104). In this study, perspectives of healthcare providers were explored for the first time on what challenged the provision of optimal healthcare and what were the future directions in caring for WWE in Palestine. This study was conducted and reported in adherence to the COREQ checklist (72). It has been argued that adherence to standard guidelines in conducting and reporting qualitative studies can improve transparency, reproducibility, and comparison/interpretation of the findings from different studies. In this study, in-depth interviews were conducted with neurologists, gynecologists, psychiatrists, internists, and clinical pharmacists. Healthcare professionals of these specialties often provide care services to WWE in Palestine. Therefore, ensuring representation of these specialties should have ensured the generation of rich qualitative data to saturate all potential themes and subthemes (8, 20, 47, 76, 104-106). The interviewees in this study were of both genders, different age groups, had a variable length of years in practice, and have frequently cared for WWE. Additionally, the interviewees worked in different healthcare establishments frequented by WWE in Palestine. Moreover, the interviewees received training in different countries. This should have enriched the qualitative data generated and analyzed in this study. In this study, thematic saturation was used as an endpoint of interviews. This adaptive method was commonly used in previous studies to a priori determine the number of interviews required for a qualitative study (8, 20, 47, 74-76, 104-107). The interviews in this study were guided by an interview schedule that was pre-validated and pilot tested. Validation and pilot testing of the interview schedule should have ensured the generation of relevant qualitative data and saturation of the major themes and subthemes (47, 108). Additionally, the qualitative data collected in this study were analyzed using the interpretative description approach (80, 81). In addition to the Leuven Qualitative Analysis Guide, this approach should have facilitated the content analysis and identification of the major themes and subthemes (82).

### 4.2.3 Current status, key challenges, and future directions in caring for WWE

Concerning women's issues, the participants stated that they would consider switching potentially teratogenic AEDs, recommend taking folic acid supplements preconceptionally, and evaluate the risks of taking versus not taking AEDs. The risks of congenital malformations as a result of using AEDs are well-established (24, 26). However, newer AEDs like lamotrigine and levetiracetam are safer for WWE of childbearing age (43, 44). International guidelines recommend WWE to use folic acid preconceptionally. Analysis of large pregnancy registries has shown an increase in the use of folic acid preconceptionally among WWE of childbearing age in the last two decades (46). In this study, the participants were aware of the importance of screening for congenital malformations. International guidelines recommend screening for congenital malformations (14, 109, 110). Apparently, the neurologists in this study adhered to the international recommendations and screened for bone health of WWE. Prescribing calcium and vitamin D supplements for WWE, especially those taking older AEDs was considered by the neurologists in this study. Vitamin D supplementation was recommended for patients with epilepsy who take AEDs including levetiracetam monotherapy (111, 112). The findings of this qualitative study showed that the clinicians recognized the existence of catamenial epilepsy among some WWE. The AEDs that the clinicians indicated they would prescribe to WWE with catamenial epilepsy were consistent with those reported in the international recommendations (113, 114). Similarly, the clinicians in this study seemed to adhere to the international guidelines in managing eclamptic seizures (115). The clinicians in this study stated that they would avoid hormones replacement therapies in WWE to avoid changes in the frequencies of seizures. Previous studies have shown that some hormonal replacement therapies can increase the frequency of seizures (116, 117). In many cases, clinicians need to carefully evaluate the benefits versus the risks of alleviating signs and symptoms of menopause using hormone replacement therapies (116). The participants in this qualitative study were aware of the effects of some AEDs on the efficacy of oral contraceptives. Healthcare providers need to counsel WWE on the optimal methods of birth control. This could help WWE avoid unintended pregnancies (118, 119). The healthcare providers who participated in this study stated that they would encourage WWE to breastfeed their infants after carefully evaluating the benefits and risks to the mother and infant. This was consistent with the international recommendations (50). It

is noteworthy mentioning that initiation and breastfeeding rates among WWE are significantly lower than their healthy counterparts (120). The participants in this study were aware of the effects of epilepsy and AEDs on the sex life of WWE. Apparently, the clinicians in this study considered counseling WWE on the use of lubricants and made referrals to psychosocial support services. Previous studies highlighted the importance of addressing sexual dysfunctions among patients with epilepsy (121).

In this study, availability, access, and affordability of neurology services were identified as a key challenge. Many healthcare systems around the world are short with neurologists and neurology services (122). It has been argued that a neurologist-based model of care for patients with epilepsy was not feasible or sustainable. Therefore, a more collaborative multi-healthcare provider approach to care for patients with epilepsy was proposed (20). In this study, the participants stated that future physicians should be encouraged to specialize in neurology. This should ensure alimenting the practice with a future workforce of neurologists. Studies conducted elsewhere showed that caring for patients with epilepsy was economically costly (123, 124). Because WWE would be more at ease disclosing and discussing their health issues with female healthcare providers, the participants stressed on the importance of increasing the availability and accessibility of female neurologists. It has been argued that the patient-healthcare provider relationship can be influenced by gender (125). Another challenge was the availability, accessibility, and affordability of new, safe, and effective AEDs. These challenges were previously shown in different healthcare systems in developing countries (126). Recent guidelines recommended the use of new safer AEDs for WWE of childbearing age (127). Awareness, knowledge, and attitudes toward epilepsy and people with epilepsy were identified as major challenges in this study. The participants called to increase awareness and knowledge and correct negative attitudes of patients themselves, healthcare providers, and the society at large about epilepsy and patients with epilepsy. The findings of this qualitative study were consistent with those reported in many previous studies (18, 40, 41). It has been suggested that awareness campaigns that would target patients, healthcare providers, and the society at large might improve awareness, knowledge, and might correct negative attitudes about epilepsy and patients with epilepsy (128). In this study, the interviewees stated that there was a need for a patient outreach system. In Palestine, patient outreach systems were lacking for many health conditions including hypertension and dyslipidemia (129, 130). Reaching out to

WWE and reminding them of their follow up visits might increase their adherence to seeking healthcare, taking their prescribed AEDs, and discussing their female-gender related issues. In this study, the participants stressed on the importance of formally adopting protocols/criteria, guidelines, and policies that would guide the diagnosis and care of patients with epilepsy. In Palestine, many protocols/criteria, guidelines, and policies that can aid healthcare providers diagnose and caring for patients were lacking (47, 129, 130).

### 4.2.4 Limitations of the study

This study is not without limitations. First, an explorative qualitative approach was used in this study. Compared to quantitative approaches, qualitative approaches are limited by design, and the qualitative data collected can be regarded as opinions of the study participants. Second, WWE were not included in this study. Considering the perspectives of the patients could have added another dimension to the perspectives of the healthcare providers interviewed in this study. However, WWE in Palestine are subjects to stigma and discrimination. Therefore, the majority of WWE would hide their diagnosis. Third, the perspectives of nurses and midwives were not collected in this study. Nurses and midwives provide large healthcare services to WWE in the Palestinian healthcare system. The inclusion of their perspectives could have been interesting. Fourth, perspectives of professional bodies, patient advocacy groups, and decision-makers in health authorities in Palestine were not collected in this study. It would have been interesting to have the voice of those stakeholders in this study.

## 4.3 Conclusions

Concentrations of AEDs can be detected in plasma or serum samples of infants who were exposed to these AEDs via breastmilk. In this review, breastmilk levels, infant plasma/serum levels, EDIs, and RIDs of AEDs were estimated/summarized. Healthcare providers and WWE might use the findings of this study to make informed decisions on the safety of breastfeeding while taking AEDs. Findings of this qualitative study showed a need to formally adopt uniform guidelines that can guide the diagnosis and care of WWE in the Palestinian healthcare system. The findings of this study might be informative to healthcare providers, decision-makers in healthcare authorities, WWE, patient advocacy groups who could be interested in improving and benchmarking

healthcare services provided to WWE. Future studies are still needed to quantitatively measure adherence to the international guidelines in caring for WWE.

In conclusion, the findings of this explorative qualitative study highlighted the key challenges for optimal healthcare of WWE in the Palestinian healthcare system from the perspectives of neurologists, gynecologists, psychiatrists, internists, and clinical pharmacists who frequently provide care for WWE. Additionally, future perspectives of the healthcare providers were also explored. The findings of this study are informative to decision-makers in health authorities, professional bodies, and patient advocacy groups who are interested in improving care of WWE in Palestine.

# List of Abbreviations

| Abbreviation | Meaning |
|---|---|
| AEDs | Antiepileptic drugs |
| COREQ | COnsolidated Criteria for REporting Qualitative Research |
| CSV | Comma-Separated Values |
| EDI | Estimated daily intake |
| FPIA | Fluorescence polarization immunoassay |
| hCG | Human chorionic gonadotropin |
| HPLC | High-performance liquid chromatography |
| IRB | Institutional Review Board |
| JBI | Joanna Briggs Institute |
| LC-MS | Liquid chromatographic-mass spectrometry |
| MeSH | Medical Subject Headings |
| MSAFP | Maternal serum α-fetoprotein |
| PRISMA | Preferred reporting items for systematic review and meta-analysis |
| PROSPERO | Prospective Register of Systematic Reviews |
| RID | Relative infant dose |
| RIS | Research Information Systems |
| RP-HPLC | Reversed-phase high-performance liquid chromatography |
| UNRWA | United Nations Relief and Works Agency |
| WWE | Women with epilepsy |

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# Appendices

## Appendix A

Adherence to PRISMA statement

| Section/topic | # | Checklist item | Section where the item was reported |
|---|---|---|---|
| **Title** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | Title |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | Abstract |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | Introduction section |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | Last paragraph of the introduction section |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Methods section |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | Methods section, section 2.3 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | Methods section. Section 2.4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Methods section 2.4 and Supplementary materials |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | Methods section, section 2.5 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | Methods section, section 2.7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Methods section, section 2.3 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | Methods section, section 2.6 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | Methods section, section 2.8 |

| Section/topic | # | Checklist item | Section where the item was reported |
|---|---|---|---|
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | n/a |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | n/a |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | n/a |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Results section and Figure 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table 1 and supplementary materials |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Results section, section 3.1 and supplementary materials |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Results section, section 3.6 and Tables |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | n/a |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | n/a |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | n/a |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Discussion section |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | Discussion section, section 4.1 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | Discussion section |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | Declarations |

## Appendix B

Example of the search strategies used in this review (PubMed/MEDLINE)

| # | Search Terms | Results (Total =7829) |
|---|---|---|
| 1 | (((((((((((((((((((((((((((((((((((((((anticonvulsants [mh ]) OR (anticonvulsive agents [tw])) OR (agents, anticonvulsive [tw])) OR (anticonvulsive drugs [tw])) OR (antiseizure drugs [tw])) OR (drugs, anticonvulsive [tw])) OR (antiseizure*[tw])) OR (anticonvulsant drugs [tw])) OR (drugs, anticonvulsant [tw])) OR (antiepileptic agents [tw])) OR (agents, antiepileptic [tw])) OR (antiepileptics [tw])) OR (brivaracetam [tw])) OR (cannabidiol [tw])) OR (carbamazepine [tw])) OR (clobazam [tw])) OR (clonazepam [tw])) OR ("eslicarbazepine acetate" [tw])) OR (ethosuximide [tw])) OR (everolimus [tw])) OR (gabapentin [tw])) OR (gabapentin [tw])) OR (lacosamide [tw])) OR (lamotrigine [tw])) OR (levetiracetam [tw])) OR (oxcarbazepine [tw])) OR (perampanel [tw])) OR (phenobarbital [tw])) OR (phenytoin [tw])) OR (piracetam [tw])) OR (pregabalin [tw])) OR (primidone [tw])) OR (rufinamide [tw ])) OR (sodium valproate [tw])) OR ("divalproex sodium"[tw])) OR (stiripentol [tw])) OR (tiagabine [tw])) OR (topiramate [tw])) OR (valproic acid [tw])) OR (vigabatrin [tw])) OR (zonisamide [tw])) AND (((((((((((((((((breast feeding [mh]) OR (feeding, breast [tw])) OR (feeding, breast [tw])) OR (breastfeeding [tw])) OR (breast feeding, exclusive [tw])) OR (exclusive breast feeding [tw])) OR (breastfeeding, exclusive [tw])) OR (exclusive breastfeeding [tw])) OR (milk, human [mh])) OR (breast milk [tw])) OR (breastmilk [tw])) OR (milk, breast [tw])) OR (human milk [tw])) OR (lactation [mh])) OR (milk secretion* [tw])) OR (lactation*, prolonged [tw])) OR (prolonged lactation* [tw])) OR (milk [mh]))) AND (((concentration* [tw]) OR (level* [tw])) OR (excretion [tw])) | Total:248<br><br>Filter: human and English=166 |

## Appendix C

The data extraction form

| # | Authors (Year) | Country in which the study was conducted | Aims/objectives of the study | Design of the study | Sample size/Data collection | Data collection method | Characteristics of the women | Drugs quantified | Analytical method | Statistical analysis | Main results | Funding information |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | |
| 3 | | | | | | | | | | | | |
| 4 | | | | | | | | | | | | |
| 5 | | | | | | | | | | | | |
| 6 | | | | | | | | | | | | |
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| 9 | | | | | | | | | | | | |
| 10 | | | | | | | | | | | | |
| 11 | | | | | | | | | | | | |
| 12 | | | | | | | | | | | | |
| 13 | | | | | | | | | | | | |
| 14 | | | | | | | | | | | | |
| 15 | | | | | | | | | | | | |

## Appendix D

The interview schedule

1. Could you please tell us about the status of care for women with epilepsy in Palestine?

**Prompts:** Where? How? Why? Could you please elaborate?

2. Could you please tell us about the protocols/guidelines/policies followed when diagnosing/caring for women with epilepsy in Palestine?

**Prompts:** Why? How? Could you please elaborate?

3. Could you please tell us about the healthcare services available for women with epilepsy in Palestine?

**Prompts:** When? How? Could you please elaborate?

4. Could you please tell us about the challenges that faces caring for women with epilepsy in Palestine?

**Prompts:** Health care system, healthcare professionals, patients, and the society? How? Why? Could you please elaborate?

5. Could you please tell how we can improve care of women with epilepsy in Palestine?

**Prompts:** What changes are needed? How? Why? Could you please elaborate?

## Appendix E

Additional information on the articles included

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
|---|---|---|---|---|---|---|---|
| 1 | Pynnonen et al. (1977) | • Samples were collected from WWE who underwent legal abortions (n = 18)<br>• Mean ages of mothers in years: group 1 (25.5 ± 6.4), group 2 (18.8 ± 3.2), group 3 (27.7 ± 7.7).<br>• The excretion of carbamazepine into the mother's milk was followed in epileptic patients with psychomotor epilepsy and grand mal epilepsy aged 21-26 years (n = 3).<br>• The milk samples from the pooled 24- hour collections of milk were treated like the plasma samples.<br>• All these mothers were concerned about a possible drug effect on their babies and therefore we analyzed the drug level in their babies. | • All these patients had had convulsions and carbamazepine had been used as symptomatic medication.<br>• The study was carried out at different dose levels in three groups each consisting of six patients: In group I the patients received 400 mg carbamazepine orally (two 200 mg commercial tablets) from 0.5 to 4.5 hours before hysterotomy. In group II the patients received the same dose from 11 to 14 hours before hysterotomy. In group III the patients received 800 mg carbamazepine or a mean of 12.2 mg/Kg divided into two doses on the day preceding abortion.<br>• All the patients received the same premedication: atropine + pethidine (meperidine) + promethazine. Anesthesia was induced with thiopentone and maintained with 70 % nitrous oxide in oxygen. A semi-open system with a respirator was used. Muscle relaxation was achieved by | • The mean concentration ratio ± S.D. of milk to mother's plasma was 0.60 ± 0.08 (n = 6) for carbamazepine, and 1.05 ± 0.45 (n = 5) for carbamazepine-epoxide.<br>• According to the mother's observations, breast feeding produced no discernible adverse effects in their infants. All the newborns were healthy and had no visible birth defects.<br>• The levels (µg/ml) of carbamazepine (CBZ) and its 10, 11-epoxide (CBZ-E) in mother's and child's plasma and in mother's milk: WWE (n = 1) treated with carbamazepine 6.0 mg/kg/day and phenytoin 4.5 mg/kg/day were 3.2 µg/mL in mother's plasma, 1.1 µg/mL in child's plasma, 1.8 µg/mL in mother's milk for carbamazepine and 0.7 µg/mL in mother's plasma, 0.3 µg/mL in child's plasma, 0.7 µg/mL in mother's milk for carbamazepine- epoxide in the second day. In the third day were 2.0 µg/mL in mother's plasma,1.3 µg/mL in child's plasma, 1.3 µg/mL in mother's milk for carbamazepine and 0.8 µg/mL in mother's plasma, 0.0 in child's plasma, 0.5 µg/mL in mother's milk for | Prospective cohort study | Gas-liquid chromatographic technic. | Not funded |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
|---|---|---|---|---|---|---|---|
| | | | an infusion of suxamethonium in 5 % glucose. During the operation pethidine was given if required. After hysterotomy 42 mg of methylergometrine (methylergonovine) was given intravenously. | carbamazepine-epoxide. After 4 weeks 3.1 µg/mL in mother's plasma ,1.8 µg/mL in child's plasma,1.8 µg/mL in mother's milk for carbamazepine and 1.1µg/mL in mother's plasma, 0.0 in child's plasma, 1.1 µg/mL in mother's milk for carbamazepine-epoxide.<br>• WWE (n = 1) treated with carbamazepine 5.8 mg/kg/day and phenytoin 2.9 mg/kg/day, the levels of carbamazepine and carbamazepine- epoxide in mother's and child's plasma and in mother's milk were 2.6 µg/mL in mother's plasma, 1.5 µg/mL in mother's milk for carbamazepine and 0.7 µg/mL in mother's milk for carbamazepine- epoxide after 3 weeks. After 5 weeks 2.6 µg/mL in mother's plasma, 0.5 µg/mL in child's plasma, 1.8 µg/mL in mother's milk for carbamazepine and 0.5 µg/mL in mother's plasma, 0.0 in child's plasma, 0.9 µg/mL in mother's milk for carbamazepine-epoxide.<br>• WWE (n = 1) treated with carbamazepine 7.3 mg/kg/day and phenytoin 2.9 mg/kg/day, mother's plasma and milk levels were 2.4, 1.5 µg/mL for carbamazepine and 0.6, 0.5 µg/mL for carbamazepine-epoxide after 3 weeks. | | | |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
|---|---|---|---|---|---|---|---|
| 2 | Nau et al. (1980) | • Samples were collected from WWE (n = 14).<br>• Blood samples were taken within 5 min after birth from epileptic women (n = 14) treated with primidone<br>• Simultaneously, blood from the umbilical artery was obtained.<br>• Blood and urine samples were collected from neonates (n = 8) and breast milk from women (n = 4) at various stages during the first weeks after birth.<br>• Following centrifugation of the blood, the serum samples obtained were frozen as soon as possible.<br>• Urine was collected quantitatively over a convenient time period (usually 8 or 24 h), the volumes were recorded and small samples were frozen.<br>• The breast milk samples were frozen as received. | • Primidone doses ranged: 1.4 mg/Kg/day- 24.8 mg/Kg/day<br><br>• Additional medications: 26.7 mg/Kg/day (valproate), 5.7 mg/Kg/day (phenytoin), 15.5 mg/Kg/day (valproate), 4.2 mg/Kg/day (phenytoin), 2.9 mg/Kg/day (ethosuximide). | • The average milk concentrations of primidone and phenylethylmalondiamide (PEMA) were about ¾, and of phenobarbital approximately ½ of the corresponding serum levels.<br>• Mean milk/serum ratio ± SD: 0.72 ± 0.15 (Primidone), 0.76 ± 0.15 (PEMA), 0.41 ± 0.16 (Phenobarbital).<br>• Milk concentrations ranged: 0.4 µg/mL - 8.2 µg/mL (primidone), 0.94 µg/mL - 2.80 µg/mL (PEMA), 0.84 µg/mL - 5.20 µg/mL (phenobarbital).<br>• Mother's serum concentrations in µg/mL ranged: 0.5 µg/mL - 10.1 µg/mL (primidone), 1.2 µg/mL - 4.0 µg/mL (PEMA), 2.6 µg/mL - 10.4 µg/mL (phenobarbital).<br>• Newborns (n = 8) were alert and had no feeding difficulties. Children (n = 6) exhibited lethargic, hypotonic and poor sucking behavior during the first 5 days. During the second and third week, two of these developed marked withdrawal symptoms with jitteriness, tremor, unmotivated crying and disturbance of sleep rhythm after they had been heavily sedated during the first days. | Cross-sectional study | Gas chromatographic--mass spectrometric system | Funded |
| 3 | Froescher et al. (1984) | • Samples were collected from WWE (n = 19) aged 20-35 years<br>• Blood and breastmilk samples were collected simultaneously or not | • Carbamazepine monotherapy was administered to WWE (n = 13) (mean dose was 13.8 ± | • The mean breastmilk carbamazepine concentration from 16 WWE was 2.5 ± 0.84 µg/mL (range 1.0 to 4.8 µg/mL<br>• On average, carbamazepine breastmilk concentrations were | Prospective cohort study | High performance liquid chromatography | Funded |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
|---|---|---|---|---|---|---|---|
| | | more than 15 min apart on 2 different days at fixed times<br>• A total of 50 breastmilk samples (21 lactation periods) were obtained between the 2nd day and 2.5 months after delivery<br>• Serum carbamazepine concentrations were determined in 7 infants 4-7 days after delivery | 5.2 mg/kg/day).<br>• Concomitant drugs: WWE (n = 3) received valproic acid, WWE (n = 2) received primidone and WWE (n = 1) received clonazepam. | 36.4 ± 8.7% (range 25% to 58.3%) of the maternal serum concentrations<br>• The mean maternal serum carbamazepine concentration from 16 WWE was 7.1 ± 1.73 µg/mL<br>• The mean serum carbamazepine epoxide concentration from 5 WWE was 2.6 ± 1.0 µg/mL<br>• The mean carbamazepine epoxide concentration in breastmilk from 5 WWE was 1.5 ± 0.4 µg/mL<br>• On average, carbamazepine epoxide breastmilk concentrations were 53 ± 13.6 % (range 34.5% - 63.3%) of the maternal serum concentrations<br>• First samples from 9 WWE were obtained between day 2 and day 8, and 2nd samples were obtained between day 3 and day 9. Of the 9 patients, 7 showed a slight increase in the relative carbamazepine content in breastmilk and a decrease was observed in 2 WWE<br>• In one WWE, there was still galactorrhea 3.5 years after delivery. The carbamazepine concentration in breastmilk was 7.7 µg/mL and 5.3 µg/mL in the maternal serum<br>• All infants had serum carbamazepine concentrations below 1.5 µg/mL | | | |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
|---|---|---|---|---|---|---|---|
| 4 | Kuhnz et al. (1984) | • Samples were collected from WWE suffered from epilepsy with primary generalized seizures (n = 10) and their infants (n = 13)<br>• Matching criteria were age of the parents, social status, parity, nicotine consumption and institution of birth.<br>• Blood samples were obtained intravenously from mother and child.<br>• Breast milk samples were taken immediately before or after blood sampling.<br>• The children were examined at birth and on the 4th day of life by a pediatrician.<br>• Neonatal behavior, such as sedation and withdrawal symptoms, was observed within the first 4 weeks after delivery, usually at the time of blood sampling and compared with behavior of the pair-matched infants as well as the group of infants who had been exposed to other AEDs than ethosuximide.<br>• Serum and milk samples were stored at -20°C until analysis. | • With one exception, all women received a combination therapy and all of them were taking their drugs already at the time of conception.<br><br>• Ethosuximide doses during pregnancy ranged between 3.5 mg/Kg/day and 23.6 mg/Kg/day.<br><br>• Comedications in mg/Kg/day: ((6.6 (carbamazepine), 0.05 (clonazepam)), (10.6 (carbamazepine), 0.03 (clonazepam)), 4.4 (phenobarbitone), 1.8 (primidone), ((6.4 (phenytoin), 0.7 (phenobarbitone)), ((11.4 (primidone), 13.6 (valproate)), 4.2 (phenytoin), 1.9 (phenobarbitone), ((34.0 (valproate), 5.7 (phenytoin)). | • Analysis of breast milk and maternal serum samples gave milk/serum concentration ratios of 0.86 + 0.08 (n = 12).<br>• The mean of ethosuximide concentration in breastmilk 49.54 (μg/mL) ± 18.68 (μg/mL)<br>• The mean of ethosuximide concentration in mother's serum 57.38 μg/mL ± 20.32 μg/mL.<br>• Two major malformations (bilateral clefting and a hare-lip) were observed.<br>• In both cases the mothers were treated with a combination of either ethosuximide/primidone or ethosuximide/phenobarbitone. | Cross-sectional prospective pair-matched, controlled study | High-performance liquid chromatography (HPLC) | Funded |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
|---|---|---|---|---|---|---|---|
| 5 | Kuhnz et al. (1988) | • Samples were collected from WWE (n = 30) and their infants (n = 35).<br>• Neonatal behavior problems, such as sedation and withdrawal symptoms were observed within the first 4 weeks after delivery, usually at the time of blood sampling.<br>• The venous blood samples were obtained from mother and child, breast milk samples were taken immediately before or after blood sampling.<br>• Serum and milk samples were stored at -20°C until analysis. | Women received phenobarbital monotherapy (n = 5), primidone monotherapy (n = 15) and received either phenobarbital or primidone in combination with other AEDs (phenytoin, ethosuximide, carbamazepine) (n = 10). | • Milk/serum concentration ratios were 0.72 ± 0.20 (n = 7) for primidone, 0.36 ± 0.09 (n = 13) for phenobarbital and 0.64 ± 0.21 (n = 6) for phenylethylmalondiamide.<br>• Fetal/maternal total serum concentration ratios were 0.88 ± 0.19 (n= 13) for primidone, 1.05 ± 0.17 (n=11) for phenylethylmalondiamide, 0.84 ± 0.18 (n=27) for phenobarbital.<br>• Infants whose mothers were receiving phenobarbital or primidone therapy showed distinct symptoms of sedation during the first 2 weeks of life.<br>• Some infants who were exposed to primidone showed withdrawal symptoms. | Cross-sectional study | A fully automated high-performance-liquid-chromatography (HPLC) system | Not funded |
| 6 | Ohman et al. (2000) | • Samples were collected from WWE (n = 9) aged 20-43 years at delivery. Women had idiopathic generalized epilepsy (n = 6), localization-related epilepsy (n = 1) and undetermined types of epilepsy (n = 2).<br>• All patients were treated with lamotrigine since before conception and were followed prospectively throughout the pregnancy.<br>• Blood samples from the mothers and from | • Lamotrigine doses in (mg/day): 800, 650, 250, 200, 600, 300, I00, 500.<br>• Concomitant AEDs: carbamazepine (100) mg/day, phenytoin (325) mg/day, carbamazepine (1400) mg/day, valproic acid (1200) mg/day.<br>• Other medications: Folic acid, hydroxocobalamin, Ferrous sulfate, promethazine hydrochloride. | • The median milk/maternal plasma lamotrigine ratio was 0.61 (range, 0.50 - 0.77) before nursing with minor changes thereafter.<br>• The minimal amount of lamotrigine ingested by the breast-fed infant was thus estimated to be ~ 0.2 mg/Kg/day - 1 mg/kg/day, assuming a daily milk intake of 150 mL/day/kg.<br>• Concentrations of lamotrigine in breast milk before nursing ranged: 2 μM - 25 μM with minor changes after nursing.<br>. Concentrations of lamotrigine in maternal plasma at delivery ranged: 3 μM – 18 μM.<br>. Median lamotrigine plasma | Cross-sectional study | Reversed-phase high-performance liquid chromatography | Funded |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
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| | | the umbilical cords were collected at delivery.<br>• After 2 weeks, when breast-feeding was established, a blood sample was drawn from the mother and the infant both at the start and after completion of breast-feeding. These plasma samples were drawn 11-15 h after the last lamotrigine dose to the mother. Intake of the morning dose of lamotrigine was delayed until after the last blood sample on the day when lactation was studied.<br>• Milk samples were obtained on the same occasion. A baseline blood sample, for comparison, was drawn from the mother 22 months before (n = 1) or after pregnancy (n = 8). | | concentrations of the nursed infants were ~30% (range, 23-50%) of the maternal lamotrigine concentrations.<br>• No adverse effects were reported in the infants. | | | |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
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| 7 | Ohman et al. (2002) | • Samples were collected from WWE (n = 5) aged 22 - 26 years at delivery<br>• Type of epilepsy: generalized, partial, undetermined.<br>• Mother–infant pairs (n = 3) were studied both at delivery and during lactation; (n =2) contributed with data from delivery only.<br>• Blood samples from the mothers and from the umbilical cords were collected at delivery.<br>• Capillary blood samples also were obtained by heel prick from the newborns on three occasions (24, 48, and 72 h) after delivery.<br>• Mother–infant pairs were studied during lactation, 2–3 weeks after delivery.<br>• Two of those also contributed with data 1 month and 3 months after delivery, respectively.<br>• After 2–3 weeks, when breast-feeding was established, a blood sample was drawn from the mothers and the infants before the morning dose, 10–15 h after the last topiramate dose to the mother. A | • Topiramate doses ranged: 100 mg/day – 400 mg/day.<br>• Concomitant AEDs: carbamazepine (800) mg/day or (1200) mg/day, valproic acid (2100) mg/day. Other medications: folic acid, flunitrazepam. | • At delivery, the umbilical/maternal topiramate plasma concentration ratios ranged from 0.85 to 1.06 (mean, 0.95).<br>• Topiramate plasma levels in the newborn declined rather rapidly.<br>• At 24 h, 3 of the infants with concentrations in the range of quantification had a mean of 40% (range, 33–45%) lower topiramate levels than those in the umbilical cord.<br>• At 48 h postpartum, topiramate plasma levels were undetectable in 2 of the infants, and 3 had detectable levels (mean, 2.1; range, 1.5–2.5 μM).<br>• The half-life was estimated to be 24 h.<br>• 3 weeks after delivery, the mean milk/maternal plasma topiramate ratio was 0.86 (range, 0.67–1.1) before nursing, with minor changes after.<br>• The weight-adjusted relative dose, assuming a daily milk in take of 150 mL/day/kg, was 3–23% of the maternal dose/day (absolute approximate dose to infant, 0.1–0.7 mg/kg/day).<br>• The plasma concentrations in 2 of the nursed infants 2–3 weeks postpartum were 1.4 and 1.6 μM, respectively.<br>• 1 infant had a topiramate concentration below the limit of detection.<br>• The concentrations in the | Cross-sectional study | Fluorescence polarization immunoassay (FPIA) | Funded |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
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| | | sample of the milk also was taken at the same time. After completion of breastfeeding, the sampling procedure was repeated. The mothers were then allowed to take the morning dose of topiramate. | | breastfed infants were 10–20% of the mothers' plasma levels.<br>• At 4 weeks, the milk/plasma ratio was 0.69 in 1 mother, and 3 months after delivery, the ratio was 0.86 6 h after dose intake in another mother. Plasma concentrations in the breast-fed infants were <0.9 μM and 2.1 μM, respectively.<br>• Breast milk concentrations were ranged between 1.6 -13.7 μM before nursing with minor changes after nursing at 2–3 weeks, 1 month, and 3 months after delivery.<br>• Mother's plasma concentrations were ranged between 2.4 – 20 μM before nursing with minor changes after nursing at 2–3 weeks, 1 month, and 3 months after delivery<br>• Nursed infant's plasma concentrations were ranged between < 0.9 – 2.1 μM before nursing with minor changes after nursing at 2–3 weeks, 1 month, and 3 months after delivery.<br>• All women had uneventful deliveries and gave birth to healthy children (no malformations were observed). | | | |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
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| 8 | Ohman et al. (2005) | • Samples were collected from WWE (n = 6) aged 22 - 42 years at delivery with their infants in which the mother was prescribed gabapentin for the treatment of epilepsy or pain disorders during pregnancy and lactation.<br>• Blood and breast milk were collected from mothers 2 to 3 weeks and, in one patient, 3 months postpartum.<br>• A sample was drawn from the mothers before the morning dose, 10–15 h after the last gabapentin dose to the mother. A sample of the milk was taken at the same time. The mothers were then allowed to take the morning dose of gabapentin. | • Gabapentin doses at time of breastfeeding ranged: 600 mg – 2100 mg daily.<br>• Concomitant AEDs: carbamazepine (1200) mg/day, lamotrigine (625) mg/day, topiramate (125) mg/day, lorazepam (2) mg/day, clonazepam (2) mg/day.<br>• Other medications: folic acid, vitamin B12, ketobemidone, enoxaparin sodium, propoxyphene, prednisolone, phenylpropanolamine, calcium, ferrous sulfate, acetaminophen, nitrofurantoin. | • At delivery, the umbilical to-maternal gabapentin plasma concentration ratios ranged from1.3 to 2.11 (mean, 1.74).<br>• Gabapentin concentrations in the neonates thereafter declined rather rapidly to, on average, 27% of the cord plasma levels (range, 12–36%) at 24 h postpartum.<br>• The umbilical cord plasma concentration was estimated to be 51 µM by extrapolation from the infant's serum concentrations.<br>• Gabapentin concentrations in breast milk and simultaneous plasma concentrations in the mothers and nursed infants were available from 5 mother–infant pairs.<br>• From 2 weeks to 3 months after delivery the mean milk/maternal plasma gabapentin ratio for sampling before nursing was 1.0 (range, 0.7–1.3).<br>• Assuming a daily milk intake of 150 mL/day/kg, the relative infant dose of gabapentin was estimated to be 0.2–1.3 mg/kg/day, which is equivalent to 1.3–3.8% of the weight-normalized dose received by the mother.<br>• At 2 to 3 weeks after delivery, 2 of the breast-fed infants had detectable concentrations of gabapentin, 1.3 and 1.5µM, respectively (under the normal range of quantification of <4 | Case series | Isocratic reversed-phase high-performance liquid chromatography (RP-HPLC) | Funded |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
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| | | | | µM), and one had an undetectable concentration.<br>• The levels of gabapentin in a plasma sample collected after 3 months of breastfeeding in another infant was 1.9 µM.<br>• The concentrations in the breast-fed infants were <12% of the mother's plasma levels and <5% of concentrations measured in the umbilical blood.<br>• Gabapentin concentrations in breast milk before nursing in (µM) :7, 51, 11, 29, 34 with respect to doses of gabapentin in mg/day: 1200, 2100, 600, 1800, 1800 and mother's plasma ranged between 10 - 45 µM.<br>• No adverse effects were reported. Although one had a premature delivery at gestational week 33, all women had uneventful deliveries and gave birth to healthy children.<br>• In one infant mild hypotonia and cyanosis developed 8 hours after birth, but the infant was discharged from hospital after 4 days in a completely normal state. | | | |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
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| 9 | Johannessen et al. (2005) | • Samples were collected from consecutive breastfeeding WWE (n = 8) aged 21 - 36 years treated with levetiracetam twice daily and their infants were studied, at delivery and/or postpartum (n = 7), and exclusively after 10 months (n = 1).<br>• Drug fasting blood samples (10–12 h after last dose) and breast milk (foremilk) were collected concomitantly at various occasions during breast-feeding.<br>• Milk/maternal serum concentrations were calculated at 3 to 5 days, and 2, 4, and 6–8 weeks postpartum in most cases, and in 2 mothers also after 4 and 10 months, respectively.<br>• Milk sample were obtained 4 weeks after levetiracetam was initiated. | WWE (n = 1) received carbamazepine (600 mg/day) and levetiracetam (3500 mg/day), (n = 1) received (1200 mg/day) carbamazepine and (1500 mg/day) levetiracetam, (n = 1) received topiramate (300 mg/day) and valproate (1800 mg/day) and levetiracetam (2000 mg/day), (n = 1) lamotrigine (200 mg/day) and levetiracetam (2500 mg/day), and (n = 1) gabapentin (1200 mg/day) and levetiracetam (2500 mg/day), (n = 2) received levetiracetam monotherapy (2000 mg/day, 3000 mg/day), breast-feeding woman (n = 1) receiving valproate and oxcarbazepine (OXC) had started treatment with levetiracetam 9 months after delivery. | • The mean milk/maternal serum concentration ratio (n=7) was 1.00 (range, 0.76–1.33) at 3 to 5 days after the delivery.<br>• The mean milk/maternal serum concentration ratios at sampling 2 (n=5), 4 (n=2), 6 to 8 weeks (n=4), and 4 and 10 months (n=2) after delivery were similar (1.10, 1.14, 1.22, 0.93, and 1.05, respectively).<br>• Levetiracetam concentrations in breast milk 3–5 days after delivery ranged from 28 μM to 153 μM.<br>• Levetiracetam maternal serum concentrations 3–5 days after delivery ranged from 28 μM to 175 μM.<br>• The infants exposed to levetiracetam had a mean birth weight of 3,650 g (range, 2,970–4,220 g) and appeared to be healthy throughout the study.<br>• Levetiracetam concentrations in infants serum 3–5 days after delivery ranged from < 10 μM to 77 μM. | Consecutive case series | An isocratic liquid chromatographic method | Not funded |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
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| 10 | Tomson et al. (2007) | • Samples were collected from WWE (n = 14) aged 21–37 years, receiving levetiracetam treatment during pregnancy and lactation contributed with 15 pregnancies.<br>• Drug levels were obtained in maternal plasma at delivery and in cord blood (n = 13).<br>• Plasma levels of levetiracetam were followed after birth in newborns (n = 13) and mother–child pairs (n = 11) were studied during breast-feeding.<br>• During pregnancy and at baseline, blood samples from the women were drawn before the morning dose. Maternal and umbilical cord blood samples were collected immediately after delivery, and are for obvious reasons thus not trough levels. Capillary blood samples were obtained from the newborns on 3 occasions during the first 2 days after birth.<br>• Blood and breast milk were collected from mothers 4–23 days after delivery. A blood sample was drawn from the mothers before the | • Levetiracetam was used as monotherapy in pregnancies (n = 6) and prescribed in combination with other AEDs during the remaining (n = 9).<br><br>• Concomitant AEDs in (mg/day) with levetiracetam dose at baseline / delivery in (mg/day): (lamotrigine (400), levetiracetam 3000/3000). (Lamotrigine (300), levetiracetam 1000/ a). (Lamotrigine (300), levetiracetam 1000/1000). (Lamotrigine (200), levetiracetam 3000/2000). (Carbamazepine (1000), levetiracetam 2500/3000). Tiagabine (30). Clobazam (45). (Oxcarbazepine (600), levetiracetam 2000/2000). (Lamotrigine (400), levetiracetam 2000/2000). (Carbamazepine (1500), levetiracetam 1000/1000). | • At delivery the umbilical cord to maternal levetiracetam plasma concentration ratio was 1.09 (range 0.64–2.0, n = 13).<br>• Levetiracetam plasma concentrations in the neonates thereafter declined to on average of 20% of the cord plasma levels (range 8–54%) at 36 h postpartum.<br>• The mean elimination half- life of levetiracetam in the neonates was 18 h (range 6–28 h).<br>• Levetiracetam concentrations in breast milk and simultaneous plasma concentration in the mothers and nursed infants were available from 11 mother–infant pairs.<br>• From 4 up to 23 days after delivery the mean milk: maternal plasma levetiracetam ratio for sampling before nursing was 1.05 (range, 0.78–1.55, n = 11).<br>• Assuming a daily milk intake of 150 mL/day/Kg the relative infant dose of levetiracetam was estimated to approximately 2.4 mg/Kg/day, which is equivalent to 7.9% of the weight normalized dose received by the mother.<br>• No adverse effects related to breast-feeding were reported.<br>• Levetiracetam (LEV) concentrations in mother's plasma before nursing ranged between 27 – 201 µmol/L and in breast milk ranged between 34 – 210 µmol/L. | Prospective cohort study | Liquid chromatographic-mass spectrometric (LC-MS) method | Funded |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
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| | | morning dose, approximately 10–15 h after the last levetiracetam dose to the mother. A sample of the milk was also taken at the same time. The mothers were then allowed to take the morning dose of levetiracetam. | | | | | |
| 11 | Newport et al. (2008) | • Samples were collected from WWE (n = 30) aged 32.2 years old (95% confidence interval [CI]: 30.0 to 34.4 years) on a stable daily dose of lamotrigine for 7 days, able to provide informed consent and their infants.<br>• All of the plasma and breast milk samples were obtained after maternal plasma lamotrigine concentrations had achieved steady state (i.e., 5 elimination half-lives), breastmilk samples were collected from the same breast by using electric or manual breast pumps for time course analysis (foremilk collected every 4 hours for 24 | • Treatment with lamotrigine was for epilepsy (63.3% [n =19]) and bipolar disorder (36.7% [n =11]).<br>• Mean of maternal daily dose of lamotrigine 386.5 mg/day (95% CI: 311.1 to 461.8 mg/day).<br>• Women and infants were taking no concomitant medications known to interact with lamotrigine metabolism or protein binding. | • The milk/plasma ratio was 41.3% (95% CI: 33.0 to 49.6).<br>• Milk/plasma ratios equaled 26.5% (95% CI: 20.2 to 32.9) when calculated by using the minimum breast milk concentration for each participant and were 2.4 times higher at 63.1% (95% CI: 47.3 to 78.9) when determined by using the maximum breast milk concentration.<br>• The mean of lamotrigine breast milk concentration 3.38 µg/mL with 95% CI (2.44 to 4.32).<br>• The mean of maternal plasma lamotrigine concentration 9 µg/mL with 95% CI (6.6 to 11.5).<br>• Elevated platelet counts (mean: 520.5 [range: 329.0 – 652.0]) were observed in 7 of 8 children | Cross-sectional study | High-performance liquid chromatography | Funded |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
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| | | hours) and foremilk-to-hindmilk gradient analysis (10-mL aliquots from a single breast).<br>• The samples were coded and stored at 80°C until assay.<br>• On average, breast milk was collected 13.0 weeks postpartum (95% CI: 7.6 to 18.4 weeks).<br>• The 210 breast milk samples were composed of 94 samples collected by 17 women for foremilk-to-hindmilk gradient analysis, 107 samples collected by 16 women for 24-hour time course analysis, and 9 spot samples. On average, breast milk was collected 13.0 weeks postpartum (95% CI: 7.6 to 18.4 weeks).<br>• Paired infant and maternal plasma samples were provided by 12 mother-infant dyads. 5 of these 12 participants did not provide breast milk samples | | | | | |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
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| 12 | Fotopoulou et al. (2009) | • Samples were collected from Caucasian WWE aged 23 – 37 years (median patients' age: 31.5 years) (n = 9)<br><br>• Patients had frontal lobe seizures that evolved into a generalized convulsive (grand-mal) seizure (n = 3); patients had a cryptogenic temporal lobe epilepsy, that evolve into secondary generalized seizures (n = 2); patient with grand-mal seizures on awakening (n = 1); patient with cryptogenic temporal lobe epilepsy (n = 1); patient with absence seizures (n = 1); and patient with idiopathic juvenile myoclonic epilepsy (n = 1).<br>• Blood samples for determination of lamotrigine serum concentration were drawn before the morning dose at an average once every 4 weeks during pregnancy, at delivery and at a mean 3 weeks after delivery (one patient was monitored even for 41 weeks in the | • Median mother's lamotrigine dosage (n = 6) 600 mg. 25% percentile 450 mg, 75% percentile 812.5 mg at delivery and the first 24 h postpartum.<br><br>• Median mother's lamotrigine dosage 350 mg, range: 250 - 900 mg. 25% percentile 300 mg. 75% percentile 637.5 mg during different stages of the postpartum period in four women on lamotrigine monotherapy.<br><br>• All patients received in addition to lamotrigine oral folate (0.6 - 1 g/daily). | • The median ratio of lamotrigine concentration in umbilical blood to maternal serum was 1.01 (interquartile (IQR) range of 25 -75$^{th}$ percentile: 0.65 - 1.12).<br>• Lamotrigine excretion into the breast milk recorded a median ratio of breast milk to maternal serum of 0.59 (IQR: 0.38 - 0.70).<br>• The values of lamotrigine concentration in breast milk decreased with the time passed after delivery.<br>• In one patient the rate of lamotrigine concentration in breast milk to maternal serum was 0.35 still almost 11 weeks after delivery.<br>• The lamotrigine serum concentration in the breastfed newborn ranged between 1.7 and 3.3 μg/mL with a median value of 2.2 μg/mL during the first 12 weeks postpartum (IQR: 2-2.7 μg/mL), corresponding to a median of 26% (IQR: 25-28%) of the maternal serum concentration (range: 18-39%).<br>• Median lamotrigine concentration in breast milk during different stages of the postpartum period in women (n = 4) on lamotrigine monotherapy 5.05 μg/mL (IQR: 3.625 μg/mL - 6.925 μg/mL).<br>• Median lamotrigine concentration in mother`s serum during different stages of the postpartum period in women (n | Prospective cohort study | Isocratic reversed-phase HPLC | Not funded |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
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| | | postpartum period). Since lamotrigine presents only a moderate protein binding capacity, we determined the total concentration values.<br>• They were able to measure the lamotrigine serum concentration in maternal and umbilical cord blood, as well as in newborn's blood at 24 and/or 48 h postpartum (n =6).<br>• They additionally ascertained the lamotrigine serum concentration in both, mother and child, as well as in breast milk (n = 4). | | = 4) on lamotrigine monotherapy 8.95 µg/mL (IQR: 8.1 µg/mL - 10.28 µg/mL). | | | |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
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| 13 | Paulzen et al. (2019) | • Samples were collected from WWE (n = 19) aged 19-39 years (mean age 30.4 ± 5.2 years; median 31 years).<br>• and newborns (n = 19)<br>• Except for one patient with a major depressive disorder, all other patients were diagnosed with localization-related idiopathic epilepsy and epileptic syndromes with seizures of localized onset.<br>• Amniotic fluid samples were available (n = 16).<br>• In breast feeding women (n=9), maternal serum samples and milk samples were acquired at the same time in a timeframe of less than 30 min and not later than 3 days after delivery.<br>• Due to clinical circumstances, a trough concentration condition for the acquisition of serum and milk samples could not be guaranteed.<br>• No dose adjustments of lamotrigine were undertaken between the time of delivery and the acquisition of serum and milk samples. | • Women received lamotrigine in daily doses between 50 and 650 mg throughout their pregnancy. The last dose adaptations took place 2 weeks before delivery.<br><br>• patients (n =3) were co-medicated with levetiracetam (500, 1000, and 3000 mg/day) throughout the whole pregnancy, whereas other patients (n = 2) were co-medicated with clobazam 25 mg/day (started some days before delivery). | • Amniotic fluid concentrations ranged between 0.5 and 8.3 µg/mL (mean 2.8 µg/mL, SD 1.9 µg/mL).<br>• Cord blood concentrations were between 1.1 and 6.2 µg/mL (mean 2.98 µg/mL, SD 1.44 µg/mL); in one case, cord blood concentrations were below the limit of quantification (0.3 µg/mL).<br>• Lamotrigine concentrations in the breast milk (n = 9) were between 1.57 and 6.1 µg/mL (mean 2.73 µg/ mL, SD 1.64 µg/mL). Associations between maternal serum and amniotic fluid ($\beta = 0.088$, $p < 0.001$, SE = 0.094) as well as umbilical cord ($\beta = 0.939$, $p < 0.001$, SE = 0.63) and breast milk ($\beta = 0.964$, $p < 0.001$, SE = 0.058).<br>• The milk: plasma ratio was in a range between 0.32 and 1.43 (mean 0.77, SD 0.35, median 0.77, Q1: 0.56, Q3: 1.00).<br>• Lamotrigine concentrations in maternal serum were in a range between 0.3 and 8.4 µg/mL, (mean 3.63 µg/ mL, SD 2.09 µg/mL). | Cross-sectional study | Isocratic high-performance liquid chromatography (HPLC) system with a UV detector | Funded |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
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| 14 | Kacirova et al. (2019a) | • Samples were collected from WWE (n = 43) aged 18 – 41 years (Mean age 27 ± 5 years), weight ranged 52 -115 Kg (Mean weight 74 ± 14 Kg)<br>• Maternal milk, maternal and infant serum levels were collected between the sixth and 33rd postnatal day (most samples were taken in the morning before the first dose).<br>• Measurement of breast milk in the first 3-to 5-day postpartum can be misleading, as its content is primarily colostrum. By the end of the first week, the milk is mature. Request forms for routine therapeutic drug monitoring were used as the data source.<br>• They analyzed milk, maternal and infant serum levels, its ratio, and the relationship between infant and milk level, maternal serum level, lamotrigine daily dose, and dose related to maternal body weight. | • Mean of the doses of lamotrigine: with neutral drugs= 269 ± 127 mg/day, with inducers= 263 ± 160 mg/day, with valproic acid= 283 ± 104 mg/day.<br>• Concomitant AEDs therapy: carbamazepine (n = 4) 600 ± 123 mg/day ranged: (450 - 750 mg/day), levetiracetam (n = 4) 2250 ± 866 mg/day ranged: (1500 - 3500 mg/day), valproic acid (n = 4) 900 ± 406 mg/day ranged: (600 - 1500 mg/day), clonazepam (n = 2) 1.75 ± 1.25 mg/day ranged: (0.5 - 3.0 mg/day), topiramate (n =1) 200 mg/day, phenytoin (n = 1) 250 mg/day. | • Lamotrigine concentrations varied from 1.1 to 14.9 mg/L in the maternal serum, from < 0.66 to 9.1 mg/L in the milk and between < 0.66 and 6.9 mg/L in the infant serum.<br>• The milk/maternal serum concentration ratio ranged from < 0.18 to 0.74, the infant/maternal serum concentration ratio between < 0.15 and 0.74, and the infant serum/milk concentration ratio between < 0.27 and 3.50.<br>• A highly significant correlation was found between milk and maternal serum levels and between infant serum levels and milk, maternal serum levels, lamotrigine daily dose, and also dose related to maternal body weight (P < 0.0001 in all).<br>• 78% of maternal Lamotrigine concentrations was found to be within the therapeutic range of 2.5–15.0 mg/L and 22% of the levels was lower.<br>• 16% of the infant's serum levels were measured to be within the therapeutic range used for the general epileptic population and 84% were lower.<br>• Lamotrigine monotherapy was prescribed in 73% of the patients, 25% of the women used bicombinations with valproic acid, carbamazepine, levetiracetam, clonazepam, or phenytoin, and 2% (1 woman) triple combination with valproic acid + topiramate. | Cross-sectional study | High-performance liquid chromatography. | Not funded |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
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| | | | | • Statistical analysis for the evaluation of drug interactions was not performed because of the small number of patients using enzyme inducing AEDs or valproic acid. | | | |
| 15 | Kacirova et al. (2019b) | • Samples were collected from nursing WWE (n = 30) aged 27 ± 5 years old<br><br>• Mature milk, maternal, and infant serum levels were collected between the sixth and 32nd postnatal day (median: 7 days, most samples were taken in the morning before the first dose) and measured between the years of 1996 and 2017.<br><br>• Measurement of breast milk in the first 3–5 days postpartum can be misleading, as its content is primarily colostrum. By the end of the first week, the milk is mature. Request forms for routine therapeutic drug monitoring were used as the data source. | • Nursing women were treated with valproic acid in monotherapy (or in combination with clonazepam) or comedicated with enzyme-inducing AEDs (phenytoin, primidone, and carbamazepine), and/or lamotrigine.<br><br>• Valproic acid monotherapy: (n = 16), mean dose 797 ± 225 mg/day, range between 300 and 1050 mg/day.<br><br>• Valproic acid + lamotrigine: (n = 3), mean dose 700 ± 87 mg/day, range between 600 and 750 mg/day.<br><br>• Valproic acid + inducers: (n = 10), mean dose 1080 ± 520 mg/day, range between 500 and 2250 mg/day.<br><br>• Total 29 women, mean dose 885 ± 369 mg/day, range between 300 and 2250 mg/day. | • Valproic acid levels varied from 5.4 to 69.0 mg/L (mean: 39.0 ± 16.1 mg/L) in the maternal serum, from < 1.0 to 16.7 mg/L (mean: 1.6 ± 3.9 mg/L) in the milk, and from < 1.0 to 17.5 mg/L (mean: 4.2 ± 4.3 mg/L) in the infant serum.<br>• The milk/maternal serum level ratio ranged between < 0.03 and 0.25 (mean: 0.03 ± 0.06) and the infant/maternal serum level ratio from < 0.03 to 0.61 (mean: 0.11 ± 0.13).<br>• No correlations were observed between maternal serum and milk levels or between maternal and infant serum levels.<br>• No significant differences were manifested for maternal daily dose, dose related to the maternal body weight, maternal clearance, milk, maternal, or infant serum valproic acid concentrations, milk/maternal serum level ratio, and infant/maternal serum level ratio between the two groups (valproic acid monotherapy versus valproic acid combination with carbamazepine, phenytoin, and/or primidone).<br>• Slightly less than a quarter | Cross-sectional study | Gas chromatography | Not funded |

| # | Authors (Year) | Sample size/Data collection | Therapy | Main results | Design of the study | Analytical method | Funding information |
|---|---|---|---|---|---|---|---|
| | | | | (23%) of maternal valproic acid concentrations was analyzed in the reference range of 50 – 100 mg/L, and 77% were lower.<br>• 67 % of milk and 33% of infant valproic acid concentrations were below the limit of quantification.<br>• None of the milk or infant serum valproic acid levels reached the lower limit of the reference range used for the population with epilepsy.<br>• Valproic acid monotherapy was prescribed in 51% of women, and 46% of the patients used bicombinations with carbamazepine, phenytoin, primidone, Lamotrigine, or clonazepam; 3% (n = 1) had a triple combination with valproic acid, lamotrigine, and topiramate. | | | |

## Appendix F

Quality appraisal for cross-sectional studies

| # | Authors (year) | Were the criteria for inclusion in the sample clearly defined? | Were the study subjects and the setting described in detail? | Was the exposure measured in a valid and reliable way? | Were objective, standard criteria used for measurement of the condition? | Were confounding factors identified? | Were strategies to deal with confounding factors stated? | Were the outcomes measured in a valid and reliable way? | Was appropriate statistical analysis used? |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Newport et al. (2008) | (+) | (+) | (+) | (+) | (+) | (-) | (+) | (+) |
| 2 | Nau et al. (1980) | (-) | (+) | (+) | (-) | (+) | (-) | (+) | (-) |
| 3 | Ohman et al. (2000) | (+) | (+) | (+) | (+) | (+) | (-) | (+) | (+) |
| 4 | Ohman et al. (2002) | (+) | (+) | (+) | (+) | (+) | (-) | (+) | (-) |
| 5 | Kacirova et al. (2019) | (+) | (+) | (+) | (-) | (+) | (-) | (+) | (+) |
| 6 | Kacirova et al. (2019) | (+) | (+) | (+) | (-) | (+) | (-) | (+) | (+) |
| 7 | Paulzen et al. (2019) | (+) | (+) | (+) | (+) | (+) | (-) | (+) | (+) |
| 8 | Kuhnz et al. (1984) | (+) | (+) | (+) | (+) | (+) | (-) | (+) | (-) |
| 9 | Kuhnz et al. (1988) | (-) | (+) | (-) | (-) | (+) | (-) | (+) | (-) |

(+): Yes/available, (-): No/not available

## Appendix G

Quality appraisal for cohort studies

| # | Author | Were the two groups similar and recruited from the same population ? | Were the exposures measured similarly to assign people to both exposed and unexposed groups? | Was the exposure measured in a valid and reliable way? | Were confounding factors identified? | Were strategies to deal with confounding factors stated? | Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? | Were the outcomes measured in a valid and reliable way? | Was the follow up time reported and sufficient to be long enough for outcomes to occur? | Was follow up complete, and if not, were the reasons to loss to follow up described and explored ? | Were strategies to address incomplete follow up utilized? | Was appropriate statistical analysis used? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Fotopoulou et al. (2009) | (-) | (-) | (+) | (+) | (-) | (+) | (+) | (+) | (-) | (-) | (+) |
| 2 | Froescher et al. (1984) | (-) | (-) | (+) | (+) | (-) | (-) | (+) | (+) | (+) | (-) | (+) |
| 3 | Pynnönen et al. (1977) | (-) | (-) | (+) | (+) | (-) | (-) | (+) | (+) | (-) | (-) | (+) |
| 4 | Tomson et al. (2007) | (-) | (-) | (+) | (+) | (-) | (+) | (+) | (+) | (-) | (-) | (+) |

(+): Yes/available, (-): No/not available

## Appendix H

Quality appraisals of case series studies

| # | Author | Were there clear criteria for inclusion in the case series? | Was the condition measured in a standard, reliable way for all participants included in the case series? | Were valid methods used for identification of the condition for all participants included in the case series? | Did the case series have consecutive inclusion of participants? | Did the case series have complete inclusion of participants? | Was there clear reporting of the demographics of the participants in the study? | Was there clear reporting of clinical information of the participants? | Were the outcomes or follow up results of cases clearly reported? | Was there clear reporting of the presenting site(s)/clinic(s) demographic information? | Was statistical analysis appropriate? |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Ohman et al. (2005) | (+) | (+) | (+) | (-) | (-) | (-) | (+) | (+) | (-) | (-) |
| 2 | Johanness en et al. (2005) | (+) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (-) | (-) |

(+): Yes/available, (-): No/not available

# Appendix I

Tables of Study

## Table I.1

*Summary of the studies included*

| # | Authors (Year) | Sample size | Type of epilepsy | Drugs | Timing of measurement | Main results | Reported adverse effects |
|---|---|---|---|---|---|---|---|
| 1 | Pynnonen et al. (1977) | WWE (n = 18) | Psychomotor and grand mal epilepsy | Carbamazepine with doses ranged from 5.8 mg/kg/day to 7.3 mg/kg/day and co-medicated with phenytoin. The doses varied from 2.9 to 4.5 mg/Kg/day. | Breastmilk samples were collected at the 2nd and 3rd day of the abortion, at 2 weeks, 3 weeks, 4 weeks, and 5 weeks after abortion. | • Carbamazepine concentrations in breastmilk ranged from 1.3 µg/mL to 1.8 µg/mL and carbamazepine epoxide ranged from 0.5 µg/mL to 1.1 µg/mL.<br>• The mean concentration ratio of breastmilk to plasma was 60.0% ± 8.0% for carbamazepine and 105% ± 45.0% for carbamazepine epoxide. | Adverse effects were not reported |
| 2 | Nau et al. (1980) | WWE (n = 14) | The types of epilepsy were not reported | Primidone with doses ranged from 1.4 mg/kg/day to 24.8 mg/kg/day.<br>The other AEDs were:<br>• Valproate (26.7 mg/kg/day and 15.5 mg/kg/day)<br>• Phenytoin (5.7 mg/kg/day)<br>• Phenytoin (4.2 mg/kg/day)<br>• Ethosuximide (2.9 mg/kg/day) | At various stages during the first weeks after birth (from the 4th day to the 27th day after birth). | • Breastmilk concentrations ranged from 0.4 µg/mL to 8.2 µg/mL (primidone), 0.94 µg/mL to 2.80 µg/mL (phenylethylmalondiamide), 0.84 µg/mL to 5.20 µg/mL (phenobarbital).<br>• The typical breastmilk concentrations of primidone and phenylethylmalondiamide were around ¾ and phenobarbital were about ½ of the corresponding serum levels, respectively. | • During the first 5 days, 6 infants were sluggish, hypotonic, and sucking poorly.<br>• After being deeply sedated during the first days, 2 infants exhibited marked withdrawal symptoms such as jitteriness, tremor, unmotivated sobbing, and sleep pattern disturbance throughout the 2nd and 3rd weeks. |

| # | Authors (Year) | Sample size | Type of epilepsy | Drugs | Timing of measurement | Main results | Reported adverse effects |
|---|---|---|---|---|---|---|---|
| 3 | Froescher et al. (1984) | WWE (n = 19) | The types of epilepsy were not reported | • Carbamazepine monotherapy was administered to WWE (n = 13) (mean dose was 13.8 ± 5.2 mg/kg/day).<br>• Concomitant drugs: 3 WWE received valproic acid, 2 WWE received primidone and 1 WWE received clonazepam. | • During the hospital stay breastmilk samples were obtained on 2 different days at fixed times.<br>• A total of 50 breastmilk samples (21 lactation periods) were obtained between the 2nd day and 2.5 months after delivery. | • The mean carbamazepine concentrations in breastmilk of 16 mothers was 2.5 μg/mL ± 0.84 μg/mL (ranged between 1.0 μg/mL and 4.8 μg/mL) and the mean carbamazepine epoxide was 1.5 μg/mL ± 0.4 μg/mL.<br>• The mean concentrations of carbamazepine and carbamazepine epoxide in breastmilk were 36.4% ± 8.7% and 53% ± 13.6% of the maternal serum concentrations, respectively. | Only 1 of 15 infants had impaired suckling |
| 4 | Kuhnz et al. (1984) | WWE (n = 10) and their infants (n = 13) | Primary generalized epilepsy | Doses of ethosuximide during pregnancy ranged from 3.5 mg/kg/day to 23.6 mg/kg/day.<br>The other AEDs were:<br>• Carbamazepine (6.6 mg/kg/day) + clonazepam (0.05 mg/kg/day)<br>• Carbamazepine (10.6 mg/kg/day) + clonazepam (0.03 mg/kg/day)<br>• Phenobarbital (4.4 mg/kg/day)<br>• Primidone (1.8 mg/kg/day)<br>• Phenytoin (6.4 mg/kg/day) + phenobarbital (0.7 mg/kg/day)<br>• Primidone (11.4 mg/kg/day) + valproate (13.6 mg/kg/day)<br>• Phenytoin (4.2 mg/kg/day)<br>• Phenobarbital (1.9 mg/kg/day)<br>• Valproate (34.0 mg/kg/day) + phenytoin (5.7 mg/kg/day) | 3rd day to 28th day after delivery. | The mean ethosuximide concentration in breastmilk was 49.54 μg/mL ± 18.68 μg/mL. | Two abnormalities (bilateral clefting and a hare-lip) were reported among the infants. Sedation with poor sucking and sleepiness were reported among 4 infants and withdrawal symptoms were reported among 5 infants |

| # | Authors (Year) | Sample size | Type of epilepsy | Drugs | Timing of measurement | Main results | Reported adverse effects |
|---|---|---|---|---|---|---|---|
| 5 | Kuhnz et al. (1988) | WWE (n = 30) and their infants (n = 35) | The types of epilepsy were not reported | Women received phenobarbital monotherapy (n = 5), primidone monotherapy (n = 15), and received either phenobarbital or primidone in combination with other AEDs (phenytoin, ethosuximide, carbamazepine) (n = 10). | Within the first 4 weeks after delivery. | Breastmilk/serum concentration ratios were 72% ± 20% (n = 7) for primidone, 36% ± 09% (n =13) for phenobarbital, and 64% ± 21% (n = 6) for phenylethylmalondiamide. | During the first 2 weeks of life, infants whose mothers were taking phenobarbital or primidone displayed characteristic sedative signs. Some of the primidone-exposed infants experienced withdrawal symptoms |
| 6 | Ohman et al. (2000) | WWE (n = 9) | Idiopathic generalized epilepsy (n = 6), localization-related epilepsy (n = 1), and unidentified types of epilepsy (n = 2) | • The doses of lamotrigine ranged from 100 mg/day to 800 mg/day<br>• Concomitant AEDs were: carbamazepine (100 mg/day), phenytoin (325 mg/day), carbamazepine (1400 mg/day), valproic acid (1200 mg/day).<br>• Other medications were: folic acid, hydroxocobalamin, ferrous sulfate, promethazine hydrochloride. | After 2 weeks, when breast-feeding was established both at the start and after completion of breast-feeding, 11-15 h after the last lamotrigine dose (from 13th to 18th day after delivery). | • Lamotrigine concentrations in breastmilk before breastfeeding ranged from 2 μM to 25 μM with negligible changes after nursing.<br>• The median breastmilk/maternal plasma lamotrigine ratio was 61% (range: 50%- 77%) before breastfeeding with negligible changes thereafter. | Adverse effects were not reported |
| 7 | Ohman et al. (2002) | WWE (n = 5) | Generalized, partial, and unidentified types of epilepsy | • Topiramate doses ranged from 100 mg/day to 400 mg/day.<br>• Concomitant AEDs were: carbamazepine (800 mg/day or 1200 mg/day) and valproic acid (2100 mg/day).<br>• Other medications included: folic acid, flunitrazepam. | After 2 weeks, when breast-feeding was established both at the start and after completion of breast-feeding, 11-15 h after the last topiramate dose (at 2–3 weeks, 1 month, and 3 months postnatal). | Topiramate breastmilk concentrations ranged from 1.6 μM to 13.7 μM before breastfeeding with negligible changes thereafter. | Adverse effects were not reported |

| # | Authors (Year) | Sample size | Type of epilepsy | Drugs | Timing of measurement | Main results | Reported adverse effects |
|---|---|---|---|---|---|---|---|
| 8 | Ohman et al. (2005) | WWE (n = 6) | The types of epilepsy were not reported | • Gabapentin doses at the time of breastfeeding ranged from 600 mg/day to 2100 mg/day.<br>• The Concomitant AEDs were:<br>• Carbamazepine (1200 mg/day)<br>• Lamotrigine (625 mg/day)<br>• Topiramate (125 mg/day)<br>• Lorazepam (2 mg/day)<br>• Clonazepam (2 mg/day) | Between 2 to 3 weeks. Samples were also obtained 3 months postpartum, before the morning dose, and 10 to15 h after the last gabapentin dose (from 12th day to 97th day after delivery). | Gabapentin concentrations in breastmilk before nursing ranged from 7 µM to 51 µM. | Mild hypotonia and cyanosis appeared in 1 infant 8 h postnatal. The infant was discharged from the hospital 4 days later in a perfectly status |
| 9 | Johannessen et al. (2005) | WWE (n = 8) | The types of epilepsy were not reported | • WWE received levetiracetam as a monotherapy (n = 2) or in combination with other AEDs (n = 6).<br>• The doses of levetiracetam ranged from 1500 mg/day to 3500 mg/day.<br>• Concomitant AEDs were: carbamazepine (600 mg/day, 1200 mg/day), topiramate (300 mg/day), valproate (1800 mg/day), lamotrigine (200 mg/day), and gabapentin (1200 mg/day). A WWE who was taking valproate and oxcarbazepine started taking levetiracetam 9 months postnatally. | During 3 to 5 days, 2 weeks, 4 weeks, and 6 to 8 weeks postnatal. Samples were also taken 4 and 10 months postnatally (10–12 h after the last dose). | • Breastmilk levetiracetam concentrations 3 to 5 days after delivery ranged from 28 µM to 153 µM.<br>• The mean breastmilk/maternal serum concentration ratio (n = 7) was 100% (range,76%–133%) at 3 to 5 days after the delivery. | Adverse effects were not reported |
| 10 | Tomson et al. (2007) | WWE (n = 14) | The types of epilepsy were not reported | • Levetiracetam was used as monotherapy for 6 pregnant WWE and as a combination with other AEDs for the other 9 WWE.<br>• Levetiracetam doses at baseline ranged from 1000 mg/day to 3000 mg/day with minor changes at delivery.<br>• Concomitant AEDs were: lamotrigine (200 mg/day to 400 mg/day), carbamazepine (1000 mg/day, 1500 mg/day), tiagabine | 4 to 23 days after delivery, before the morning dose, and approximately 10 to15 h after the last levetiracetam dose. | • Levetiracetam concentrations in breastmilk ranged from 34 µmol/L to 210 µmol/L.<br>• The mean of breastmilk: maternal plasma levetiracetam ratio was 105% (range: 78%–155%, n = 11). | Adverse effects were not reported |

| # | Authors (Year) | Sample size | Type of epilepsy | Drugs | Timing of measurement | Main results | Reported adverse effects |
|---|---|---|---|---|---|---|---|
| | | | | (30 mg/day), clobazam (45 mg/day), and oxcarbazepine (600 mg/day). | | | |
| 11 | Newport et al. (2008) | n = 30) | Epilepsy (63.3% [n =19]) and bipolar disorder (36.7% [n =11]) | The mean of maternal daily dose of lamotrigine was 386.5 mg/day (95% CI: 311.1 mg/day to 461.8 mg/day). | On average, breastmilk samples were collected at 13 weeks postpartum (95% CI: 7.6 to 18.4 weeks). | The mean of lamotrigine breastmilk concentration was 3.38 µg/mL (95% CI: 2.44 µg/mL to 4.32 µg/mL) and the breastmilk/plasma ratio was 41.3% (95% CI: 33.0% to 49.6%). | Elevated platelet counts (mean: 520.5 [range: 329.0 – 652.0]) were observed in 7 of 8 infants. No significant clinical implications were noted |
| 12 | Fotopoulou et al. (2009) | WWE (n = 9) | Frontal lobe seizures that progressed to a generalized convulsive (grand-mal) seizure (n = 3), WWE with cryptogenic temporal lobe epilepsy that progressed to secondarily generalized seizures (n = 2), a WWE with grand-mal seizures on waking up (n = 1), a WWE with absence seizures (n = 1), and a | • WWE received lamotrigine monotherapy and oral folate (0.6 - 1 g/daily).<br>• The median lamotrigine dose in 6 WWE was 600 mg/day at delivery and the first 24 h postnatal.<br>• The median lamotrigine dose was 350 mg/day (range: 250 to 900 mg/day) during different stages of the postpartum period in 4 WWE who were on lamotrigine monotherapy. | During different stages of the postpartum period (from 2 weeks to 12 weeks). | • The median lamotrigine concentration in breastmilk was 5.05 µg/mL (interquartile range: 3.625 µg/mL to 6.925 µg/mL).<br>• The median lamotrigine breastmilk to maternal serum ratio was 59% (interquartile range: 38% to 70%). | Adverse effects were not reported |

| # | Authors (Year) | Sample size | Type of epilepsy | Drugs | Timing of measurement | Main results | Reported adverse effects |
|---|---|---|---|---|---|---|---|
| | | | patient with idiopathic juvenile myoclonic epilepsy (n = 1) | | | | |
| 13 | Paulzen et al. (2019) | WWE (n = 19) | Except for one patient who suffered from major depression, all of the other patients had idiopathic epilepsy and epileptic disorders with localized onset seizures | • WWE received lamotrigine in daily doses of 50 mg to 650 mg throughout their pregnancy.<br>• WWE (n = 3) in the study were co-medicated with levetiracetam (500 mg/day, 1000 mg/day, and 3000 mg/day) throughout their pregnancy.<br>• Other patients (n = 2) were co-medicated with clobazam 25 mg/day (started some days before delivery). | In the period between less than 30 min and no longer than 3 days following delivery. | • Lamotrigine breastmilk concentration ranged from1.57 µg/mL to 6.1 µg/mL (mean: 2.37 µg/mL ± 1.64 µg/mL).<br>• The breastmilk to plasma ratio ranged from 32.0% to 143% (mean: 77.0% ± 35.0%, median 77.0%, first quartile: 56.0%, third quartile: 100.0%). | Adverse effects were not reported |
| 14 | Kacirova et al. (2019a) | WWE (n = 43) | The types of epilepsy were not reported | • The mean lamotrigine dose with neutral drugs was 269 mg/day ± 127 mg/day, with inducers was 263 mg/day ± 160 mg/day, and with valproic acid was 283 mg/day ± 104 mg/day.<br>• The concomitant AEDs were:<br>• Carbamazepine (4 WWE) (mean: 600 ± 123 mg/day, range: 450 - 750 mg/day)<br>• Levetiracetam (4 WWE) (mean: 2250 ± 866 mg/day, range: 1500 - 3500 mg/day)<br>• Valproic acid (4 WWE) (mean: 900 ± 406 mg/day, range: 600 - 1500 mg/day)<br>• Clonazepam (2 WWE) (mean: 1.75 ± 1.25 mg/day, range: 0.5 - 3.0 mg/day) | Between the 6th and the 33rd postpartum day, (most of the samples were collected in the morning before receiving the first dose). | • Lamotrigine concentrations in breastmilk ranged from < 0.66 mg/L to 9.1 mg/L.<br>• The breastmilk/maternal serum concentration ratio ranged from < 18% to 74%. | Adverse effects were not reported |

| # | Authors (Year) | Sample size | Type of epilepsy | Drugs | Timing of measurement | Main results | Reported adverse effects |
|---|---|---|---|---|---|---|---|
| | | | | • Topiramate (1 WWE) (200 mg/day)<br>• Phenytoin (1 WWE) (250 mg/day) | | | |
| 15 | Kacirova et al. (2019b) | (n = 30) | The types of epilepsy were not reported | • Women were treated with valproic acid in monotherapy (or in combination with clonazepam), co-medicated with enzyme-inducing AEDs (phenytoin, primidone, and carbamazepine), and/or lamotrigine.<br>• The mean dose of valproic acid was 885 mg/day ± 369 mg/day (range: 300 mg/day to 2250 mg/day). | Between the 6th and 32nd postpartum days (median: 7 days; most samples were collected in the morning before the first dose). | Valproic acid levels in the breastmilk ranged from 1.0 mg/L to 16.7 mg/L (mean = 1.6 ± 3.9 mg/L) | Adverse effects were not reported |

**Table I.2**

*Breastmilk concentrations of antiepileptic drugs*

| # | Drug | Breastmilk concentration | Maternal plasma concentration | Maternal serum concentration | Breastmilk/maternal plasma ratio (%) | Breastmilk/maternal serum ratio (%) | Infant plasma concentration | Infant serum concentration | Infant/maternal serum ratio (%) | Infant/maternal plasma ratio (%) | Infant serum/breastmilk ratio (%) | Infant plasma/breastmilk ratio (%) | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Carbamazepine | 2.5 ± 0.84 µg/mL (range: 1.0 – 4.8 µg/mL) | – | 7.1 ± 1.73 µg/mL | 36.4 ± 8.7 | – | – | < 1.5 µg/mL | < 21.1 | – | < 60 | – | Froescher et al. (1984) |
| 2 | Carbamazepine epoxide | 1.5 ± 0.4 µg/mL | – | 2.6 ± 1.0 µg/mL | 53.0 ± 13.6 | – | – | – | – | – | – | – | Froescher et al. (1984) |
| 3 | Carbamazepine | 1.62 µg/mL (range: 1.3 – 1.8 µg/mL) | 2.65 µg/mL | – | 60.0 ± 8.0 | – | 1.18 µg/mL | – | – | 44.5 | – | 72.8 | Pynnonen et al. (1977) |
| 4 | Carbamazepine epoxide | 0.73 µg/mL (range: 0.5 – 1.1 µg/mL) | 0.74 µg/mL | – | 105 ± 45 | – | 0.08 µg/mL | – | – | 10.8 | – | 11.0 | Pynnonen et al. (1977) |
| 5 | Lamotrigine | 2.73 ± 1.64 µg/mL (range: 1.57 – 6.1 µg/mL) | – | 3.63 ± 2.09 µg/mL | 77 ± 35 (range 32% to 143%) | – | – | – | – | – | – | – | Paulzen et al. (2019) |
| 6 | Lamotrigine | 3.38 µg/mL (95%CI: 2.44 – 4.32 µg/mL) | 9 µg/mL (95%CI: 6.6 – 11.5 µg/mL) | – | 41.3 (95%CI: 33.0 – 49.6) | – | – | – | – | – | – | – | Newport et al. (2008) |
| 7 | Lamotrigine | 2 µM – 25 µM, mean = 12.9 ± 6.97 µM | 3 µM – 18 µM | – | Median = 61 (range, 50 – 77) | – | – | – | – | Median = 30 (range, 23–50) | – | – | Ohman et al. (2000) |

| # | Drug | Breastmilk concentration | Maternal plasma concentration | Maternal serum concentration | Breastmilk/maternal plasma ratio (%) | Breast milk/maternal serum ratio (%) | Infant plasma concentration | Infant serum concentration | Infant/maternal serum ratio (%) | Infant/maternal plasma ratio (%) | Infant serum/breastmilk ratio (%) | Infant plasma/ breastmilk ratio (%) | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | Lamotrigine | < 0.66 – 9.1 µg/L (mean: with inducers = 0.8 ± 0.6 µg/mL, with valproic acid = 5.4 ± 4.9 µg/mL, with neutral drugs = 2.8 ± 2.2 µg/mL | – | 1.1 – 14.9 µg/L | – | < 18 – 74 | – | < 0.66 and 6.9 µg/L | < 15 and 74 | – | < 27 – 350 | – | Kacirova et al. (2019) |
| 9 | Lamotrigine | Median = 5.05 µg/mL (IQR: 3.625 µg/mL – 6.925 µg/mL). Mean= 5.19 µg/ml | – | Median = 8.95 µg/mL (IQR: 8.1 – 10.28 µg/mL) | – | 59 (IQR: 38 – 70) | – | Median= 2.2 µg/mL (IQR: 2– 2.7 µg/mL | 26 (IQR: 25–28) | – | 43.6 | – | Fotopoulou et al. (2009) |
| 10 | Topiramate | ranged between 1.6 – 13.7 µM | 2.4 – 20 µM | – | 86 (range, 67–110) | – | < 0.9 – 2.1 µM | – | – | 10 – 20 | 15.3 – 56.3 | – | Ohman et al. (2002) |
| 11 | Gabapentin | 26.4 µM (range 7– 51 µM) | 10 – 45 µM | – | 100 (range, 70 – 130) | – | 1.6 µM (range: 1.3 – 1.9 µM) | – | 4.2 – 13.0 | < 12 | – | 3.7 – 18.6 | Ohman et al. (2005) |
| 12 | Valproic acid | 1.6 ± 3.9 mg/L | – | 39.0 ± 16.1 mg/L | – | 30 ± 6 | – | 4.2 ± 4.3 mg/L | 11 ± 13 | – | 262.5 | – | Kacirova et al. (2019) |
| 13 | Ethosuximide | 49.54 (µg/mL) ± 18.68 (µg/mL) | – | 57.38 µg/mL ± 20.32 | – | 86 ± 8 | – | 5 µg/mL – 34 µg/mL | 8.7 – 59.3 | – | 1 – 68.6 | | Kuhnz et al. (1984) |

| # | Drug | Breastmilk concentration | Maternal plasma concentration | Maternal serum concentration | Breastmilk/maternal plasma ratio (%) | Breast milk/maternal serum ratio (%) | Infant plasma concentration | Infant serum concentration | Infant/maternal serum ratio (%) | Infant/maternal plasma ratio (%) | Infant serum/breastmilk ratio (%) | Infant plasma/ breastmilk ratio (%) | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | µg/mL | | | | | | | | | |
| 14 | Levetiracetam | 28 µM – 153 µM | – | 28 µM – 175 µM | – | 100 (range: 76 – 133) | – | < 10 µM – 77 µM | 35.7 – 44.0 | – | 35.7 – 50.3 | – | Johannessen et al. (2005) |
| 15 | Levetiracetam | 34 – 210 µmol/L | 27 – 201 µmol/L | – | 105 (range, 78–155) | – | – | – | – | – | – | – | Tomson et al. (2007) |
| 16 | Primidone | 0.4 µg/mL – 8.2 µg/mL (Mean = 4.15 µg/mL) | – | 0.5 µg/mL – 10.1 µg/mL (Mean = 6.09 µg/mL) | – | 72 ± 15 | – | 0.8 µg/mL – 1 µg/mL | 10 | – | 12.2 – 200 | – | Nau et al. (1980) |
| 17 | Phenylethylmalondiamide | 0.94 µg/mL – 2.80 µg/mL (Mean = 1.96 µg/mL) | – | 1.2 µg/mL – 4.0 µg/mL (Mean = 2.72 µg/mL) | – | 76 ± 15 | – | 0.5 µg/mL – 0.6 µg/mL | 15 | – | 21.4 – 53.2 | – | Nau et al. (1980) |
| 18 | Phenobarbital | 0.84 µg/mL – 5.20 µg/mL (Mean = 2.85 µg/mL) | – | 2.6 µg/mL – 10.4 µg/mL (Mean = 6.13 µg/mL) | – | 41 ± 16 | – | 1.5 µg/mL – 3 µg/mL | 30 | – | 57.7 – 178.6 | – | Nau et al. (1980) |
| 19 | Primidone | – | – | – | – | 72 ± 20 | – | – | 88 ± 19 | – | – | – | Kuhnz et al. (1988) |

| # | Drug | Breastmilk concentration | Maternal plasma concentration | Maternal serum concentration | Breastmilk/maternal plasma ratio (%) | Breast milk/maternal serum ratio (%) | Infant plasma concentration | Infant serum concentration | Infant/maternal serum ratio (%) | Infant/maternal plasma ratio (%) | Infant serum/breastmilk ratio (%) | Infant plasma/ breastmilk ratio (%) | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 20 | Phenylethylmalondiamide | – | – | – | – | 64 ± 21 | – | – | 105 ± 17 | – | – | – | Kuhnz et al. (1988) |
| 21 | Phenobarbital | – | – | – | – | 36 ± 9 | – | – | 84 ±18 | – | – | – | Kuhnz et al. (1988) |

جـامعـــة النجاح الوطنية

كليـــة الدراســـات العليـــا

# العلاج الدوائي للصرع عند النساء: الوضع الحالي والاتجاهات المستقبلية والتحديات

إعداد

لينا عزمي مصطفى زيد

إشراف

د. رمزي شواهنه

قدمت هذه الرسالة إستكمالاً لمتطلبات الحصول على درجه الماجستير في علم الأدوية، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس– فلسطين.

2022

# العلاج الدوائي للصرع عند النساء: الوضع الحالي والاتجاهات المستقبلية والتحديات

**إعداد**

**لينا عزمي مصطفى زيد**

**إشراف**

**د. رمزي شواهنه**

## الملخص

**خلفية الدراسة:** أجريت هذه الدراسة على مرحلتين: مراجعة منهجية ودراسة نوعية. أجريت المراجعة المنهجية لتقييم تراكيز الأدوية المضادة للصرع في حليب الأمهات المرضعات المصابات بالصرع. أجريت الدراسة النوعية لتبيان وجهات نظر أطباء الأعصاب وأطباء النسائية والأطباء النفسيين وأطباء الباطنة والصيادلة فيما يتعلق برعاية النساء المصابات بالصرع في فلسطين.

**منهجية الدراسة:** تم البحث بشكل منهجي في قواعد البيانات التالية: MEDLINE/PubMed وEMBASE وCINAHL/EBSCO وCOCHRANE وSpringerLink وScienceDirect وSummon وWHO International Clinical Trials Registry Platform وSCOPUS. أجريت مقابلات مع ستة أطباء أعصاب، وخمسة أطباء أمراض نسائية، وثلاثة أطباء نفسيين، وطبيب الباطني، وخمسة صيادلة سريريين. تم استخدام منهجية الوصف التفسيري لتحليل البيانات النوعية بشكل موضوعي.

**نتائج الدراسة:** هذه المراجعة المنهجية شملت ما مجموعه 15 دراسة. أفادت الدراسات المشمولة بمستويات 8 أدوية مضادة للصرع في حليب الأمهات المصابات بالصرع. لاموتريجين، ليفيتيراسيتام، كاربامازيبين، توبيراميت، حمض فالبرويك، وجابابنتين لم يتسببو بتأثيرات ضارة كبيرة تستدعي التوقف عن الرضاعة الطبيعية. ينصح بوقف الرضاعة الطبيعية أو تقليلها في حال ظهورعلامات النعاس المفرط و/أو نزول الوزن عند الرضع المعرضين للبريميدون والفينوباربيتال، أو إيثوسكسيميد/ بريميدون، أو إيثوسكسيميد/

فينوباربيتال. ظهرت الموضوعات التالية من البيانات النوعية: 1) ضرورة التشخيص وتقديم الرعاية لمرضى الصرع، 2) الإهتمام بأبرز القضايا العامة في رعاية مرضى الصرع، 3) مراعاة قضايا المرأة في العلاج الدوائي للصرع. لم تكن هناك بروتوكولات/معايير معتمدة رسميًا لتشخيص ورعاية النساء المصابات بالصرع. تم تجميع التحديات الحالية والتوجهات المستقبلية في رعاية النساء المصابات بالصرع تحت نظام رعاية صحية متكامل ويشمل مقدمي الرعاية الصحية والمرضى والمجتمع. كانت زيادة وصول النساء المصابات بالصرع إلى خدمات طب الأعصاب المتخصصة وتحسين القبول في المجتمع هي الاتجاهات المستقبلية الرئيسية.

**الخلاصة:** نتائج هذه الدراسة قد تكون ذات فائدة لقطاع الرعاية الصحية والنساء المصابات بالصرع وتساهم في تقديم المساعدة في إتخاذ قرارات سليمة بشأن سلامة الرضاعة الطبيعية أثناء تناول أدوية الصرع. أظهرت نتائج الدراسة النوعية الحاجة إلى اعتماد إرشادات موحدة رسميًا يمكن أن توجه تشخيص ورعاية النساء المصابات بالصرع في نظام الرعاية الصحية الفلسطيني.

**كلمات مفتاحية:** الأدوية المضادة للصرع، الرضاعة الطبيعية، الصرع، حليب الأم، الرضاعة، النساء.