Children of Mothers with Epilepsy Exposed to Antiepileptic Drugs During Pregnancy. Long-term Neurocognitive and Behavioral Functioning from a Family Perspective

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Summary and discussion
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This dissertation shows that the use of antiepileptic drugs (AEDs) in women with epilepsy of childbearing age needs continuous attention, also in light of long-term outcomes in children \(^1-^3\). Treatment continuation during pregnancy is a must for most women with active epilepsy \(^4\), whereas prenatal exposure to AEDs is associated with increased risks of congenital malformations \(^5\), which indicates the associated challenges of AED use. In the past two decades, more attention has also been paid to possible long-term effects of prenatal exposure to AEDs \(^6-^8\). However, in order to help women and their treating physicians to make a well-informed choice on medication use during pregnancy, still more information is needed, specifically on newer AEDs, the potential spectrum of developmental side effects, and the role of factors modifying the teratogenic risks and eventual outcome \(^3,^6-^9\).

The aim of this thesis therefore was to obtain more knowledge about the long-term effects of prenatal exposure to four common AED monotherapies (valproate, carbamazepine, lamotrigine or levetiracetam) on the neurocognitive and behavioral development of school-aged children. We developed the Dutch EURAP & Development study protocol and described the extensive neuropsychological child assessment at six or seven years of age (Chapter 1). The nature and severity of neurocognitive and behavioral problems was examined in relation to prenatal exposure and possible effects of AED dose (Chapter 3, 4 and 5). The contribution of distinct family factors in maternal epilepsy, a chronic medical condition, has also been investigated (Chapter 2 and 6), including a description of the wellbeing of mothers with epilepsy (Chapter 7).

Neurocognitive profiles

Based on the findings reported in Chapter 3 and results on social cognition in Chapter 5, we made neurocognitive profiles by AED exposure group, while controlling for the effect of maternal IQ.

VPA-exposed children \((n = 22)\) performed worse in all neurocognitive domains when compared to children exposed to CBZ \((n = 32)\), LTG \((n = 82)\), or LEV \((n = 25)\), especially on language skills \((9-13\) points lower on verbal IQ \((VIQ))\). Children exposed to VPA had more problems with verbal functioning \((general\ knowledge,\ abstract\ reasoning,\ and\ understanding\ social\ rules\ and\ concepts)\). They are less able to understand spoken language, are slower in retrieving semantic access to words and make more mistakes in the production of words. They have less ability to generate words and have a smaller vocabulary. In addition, inhibition and motor persistence \((Statue)\) which is an indicator
of school readiness, was impaired. Difficulties in finger movements and in paper and pencil tasks may be an indication of immature fine motor skills. Children also have difficulty with Memory for Faces, which has been found to be associated with pervasive social perception problems\textsuperscript{10}. On tasks of social cognition, valproate-exposed children had more difficulty with recognizing and comparing emotions and performed significantly lower on Theory of Mind tasks compared to the other AED-exposed children. We observed that children exposed to VPA seemed in some way more childish. This is consistent with frequent repeating a year at school and the reported additional educational needs. These findings correspond with previous observational studies\textsuperscript{11–17}, which also found an association between VPA exposure and lower verbal IQ, and difficulties with attention and memory. A recent Danish population study showed an association between VPA exposure and long-term academic functioning, which may reflect the lower performances seen in observational studies\textsuperscript{18}.

Children exposed to CBZ had few problems with neurocognitive functioning. On cognitive functioning (intelligence) they had average scores. Compared to VPA they were verbally stronger, otherwise they had comparable IQ scores. They performed well on Memory for Faces, especially on Memory for Faces Delayed, with an above-average score, which was significantly higher compared to LTG- and VPA-exposed children. On the other hand, they performed somewhat slower on Visuomotor Coordination and significantly lower on the Verbal Fluency task (Lindeboom) (CBZ < LTG). On other neurocognitive tasks, CBZ-exposed children achieved average scores. Compared to VPA-exposed children they achieved both higher scores, as well as comparable scores. They differed from each other on tasks of attention and executive functions, language, memory, visual spatial skills and to a lesser extent on motor skills. These results are in line with previous observational studies, showing normal intelligence and few problems with neurocognitive functioning after prenatal CBZ exposure\textsuperscript{6,11,13,14}.

The largest group of children within our cohort was prenatally exposed to LTG (n = 82). LTG-exposed children had little to no problems with neurocognitive functioning and showed to be verbally strong. They had in general average scores, with no below-average scores at group level. Compared to VPA-exposed children they scored generally higher, with a number of significant differences in intelligence, language, attention and executive functioning, visual spatial skills and fine motor skills. We found virtually no significant differences between LTG- and CBZ- or between LTG- and LEV-exposed children, they had comparable performances. Previous observational studies on
neurocognitive functioning of LTG-exposed children at school-age showed similar results, finding little to no problems\textsuperscript{6,11,14,19,20}.

LEV-exposed children appeared to be cognitively strong, especially on verbal functioning, with an above average VIQ on group level. 28\% of LEV-exposed children had a disharmonic profile (more than 16 points difference in VIQ vs PIQ scores) in favor of verbal IQ (VIQ > PIQ), while only 4\% showed an inverse profile (PIQ > VIQ). This was opposite from the intelligence profiles seen in VPA-exposed children, who were more likely to have a higher performance IQ (18\% PIQ > VIQ vs 9\% VIQ > PIQ). A previous observational study in the UK on LEV-exposed children in school-age (n = 42), did not find increased verbal intelligence scores\textsuperscript{12}. In our study, LEV-exposed children showed few problems with neurocognitive functioning. Their language skills seemed very well developed, with a strong understanding of spoken language, a great vocabulary and good word production. On Speeded Naming however, they made in comparison with peers more mistakes. On tasks of attention and executive functioning, memory and learning, fine motor skills and visuospatial skills LEV-exposed children usually achieved average or above-average scores. Their graphomotor skills seemed only a little less, where they performed slightly lower and made more mistakes compared to LTG-exposed children and compared to peers (Visuomotor Coordination). This can be related to the younger age as well as impulsive behavior\textsuperscript{10}. On other tasks there were no significant differences between LEV- and LTG-exposed children. There were some differences between LEV- and CBZ-exposed children (e.g., verbal IQ), but after controlling for maternal IQ, these results became non-significant, illustrating the importance of maternal IQ in evaluating cognitive outcome of the offspring. Compared to VPA-exposed children, LEV-exposed children performed better in all neurocognitive domains, with significant differences on language skills and attention and executive functioning. The few earlier studies that have examined LEV-exposed children showed no impairments in neurocognitive development and IQ, and higher performances compared to VPA-exposed children\textsuperscript{12,21}. Our group of LEV-exposed children, however, was small (n = 25), so results should be interpreted with caution.

**Behavioral problems**

In Chapter 4 we examined behavioral functioning of prenatal AED-exposed children. Mothers and fathers completed behavioral questionnaires on child behavior problems such as anxiety, depression, attention, oppositional defiant and aggressive behavior. We found, against expectation, that all four AED exposure groups showed high percentages of children with clinical behavioral problems, with
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total behavioral problems occurring in 32% of VPA-exposed children (n = 26), 14% of CBZ- (n = 37),
16% of LTG- (n = 88) and 14% of LEV-exposed children (n = 30). VPA-exposed children were shown
to be most affected, but parents of CBZ-, LTG-, and LEV-exposed children also reported behavioral
problems within the clinical range. Children differed on the range of behavioral problems, without a
common single subphenotype.

Children appeared to have internalizing and externalizing problems. Parents of LTG-exposed
children frequently reported oppositional defiant behavior within the clinical range (ODD). Compared
to Dutch population norms, parents of VPA-, LTG-, and LEV-exposed children reported significantly
more often symptoms of conduct disorder (CD). Autistic behavior was reported by parents in VPA-
and LTG-exposed children. CBZ-exposed children showed no higher proportion of clinical behavioral
problems. No differences in proportions were found for parent-report of ADHD or anxious behavior.

Analyses with unadjusted means revealed no significant differences between the AED-
exposure groups. After controlling for potential confounders (including maternal behavioral problems)
VPA-exposed children showed significantly more social problems compared to LTG- and LEV-
exposed children, and significantly more attention problems compared to LEV-exposed children. No
significant differences were found on the other (sub)scales. A direct comparison between LTG and
LEV showed few differences. LTG-exposed children were only found to have significantly more
attention deficit problems, but significantly less anxiety. LTG- and LEV-exposed children differed but
had average mean scores – compared to Dutch population norms – on attention and anxiety
problems.

Previous studies also reported significantly more behavioral difficulties in prenatally AED
exposed children of mothers with epilepsy, when compared to non-exposed children and children of
mothers without epilepsy\textsuperscript{22}, including children exposed to CBZ or LTG\textsuperscript{23,24}. Other studies only found
increased behavioral problems in VPA-exposed children\textsuperscript{25-30}. The few studies that have been done,
differ on methodology and age of the children, and used different rating scales, which may explain the
different results on behavior.

We used parent-reports, which clearly reflects the child’s behavior parents experience at
home. Parent-report is, however, subjective and does not directly correspond with a diagnosis made
by professionals\textsuperscript{24}. Parents are also not blinded for AED exposure and therefore concerns about
teratogenic effects could have inflated their ratings. This does not, however, detract from the fact that
parents seem to have concerns about the behavioral development of their children\textsuperscript{24}. It is therefore important to pay attention to these reported behavioral problems and also to consider other contributing factors, such as the impact of maternal epilepsy on child development, as multiple risk factors (including teratogenic effects of prenatal AED exposure and family factors) may contribute to child behavioral problems.

\textit{Autism}

When specific autism characteristics were examined (Chapter 5) we found that VPA-exposed children compared to those exposed to CBZ, LTG or LEV scored significantly higher on the clinician observation ratings of symptoms of autism (CARS2-HF-NL). These results are consistent with earlier reports on autistic traits and increased risk of autism spectrum disorders (ASD) in prenatal VPA exposed children\textsuperscript{24,28,29,31,32}.

In our study no children scored within the severe category of the CARS2-HF-NL. It seemed that VPA-exposed children had autistic traits, but they may not always meet the criteria of a diagnosis of autism. This might be because our group of children was higher functioning (with average intelligence), and we perhaps missed severe cases\textsuperscript{32,33}, or there may be a broader spectrum of developmental teratogenicity after prenatal VPA exposure. On the basis of clinical observations, children exposed to VPA seemed to have a particular development, with a specific neurocognitive profile (see above) and certain behavioral characteristics. In many cases children functioned well, but in some aspects, they appeared atypical compared to healthy developing children, which is important to be mentioned. Research on children with fetal valproate syndrome have also shown a specific (cognitive) profile and possible associations with autism\textsuperscript{31,33–36}. We noticed sometimes also dysmorphic features in the face (such as lower ears, broader nasal bridge, long philtrum, small lips) in prenatally VPA-exposed children. Investigation and analysis of dysmorphic features was however not part of the current study.

In accordance with other studies, only a part of the children exposed to VPA seem to experience problems. It remains unclear why some children are affected by prenatal VPA exposure and others are not. Susceptibility for possible gene-environment interactions seems to play a role\textsuperscript{37}. In animal studies on associations between prenatal VPA exposure and neural tube defects it was observed that the exposure affected gene expressions. It was suggested that although a single change may be developmentally harmless, several genes or gene expression alterations together
may produce the adverse phenotypic changes that result in the observed neural tube defects\(^3^7\). It is possible that similar mechanisms associated with neural tube defects also underlie the broader developmental teratogenesis of VPA, including the observed increased risk of autism. It seems in any case clear that multifactorial etiologies, with genetic and environmental components, contribute to long-term observed development problems\(^3^7\)–\(^3^9\). More research is needed on the biomolecular basis including possible gene-teratogen interactions\(^3^8\)–\(^4^1\).

Since a child is exposed to various genetic and environmental factors, both during pregnancy as well as thereafter in growing up within a family, it remains difficult to separate cause and effect, and this problem increases with longer duration of follow-up. Nevertheless, this and previous studies with and within different populations have consistently shown that prenatal exposure to VPA, especially at doses higher than 800-1,000 mg/day, is associated with a greater risk of congenital malformations, cognitive problems and autism\(^5\),\(^1^1\),\(^1^4\),\(^2^9\). It is important that women with epilepsy, but also women who use VPA for other indications (mood disorders, migraine), are properly informed of the risks and that alternatives like change of medication type or reduction of dose are considered and discussed and applied whenever possible\(^4^2\)–\(^4^4\). We also stress that comparison of different maternal indications for the same drug, like epilepsy, migraine, mood disorders, and pain disorders may help to sort out the confounding by indication issues.

**Confounding factors for outcome of neurocognition, behavior and autism**

In the above-discussed findings, the possibility of confounding bias is an important component to consider\(^4^5\). Confounding bias is a function of the complex interrelationship between different exposures and the outcome measures\(^4^6\). In our study we therefore took various potential confounding factors into consideration, such as maternal IQ or maternal behavioral problems (Chapter 1, 3, 4 and 5).

In research on prenatally AED-exposed children of mothers with epilepsy, confounding by indication is also an important potential confounder\(^4^6\). This means that certain types of epilepsy, with increased risks of developmental problems by itself, may be treated specifically with certain AEDs, resulting in a spurious association between prenatal AED exposure and cognitive or behavioral outcome measures. Although in our observational design it is difficult to exclude confounding by indication, we found no clear evidence for an association between type of epilepsy and cognitive or behavioral problems in prenatally AED-exposed children of mothers with epilepsy. Type of AED used
during pregnancy differed significantly by type of epilepsy, but because type of epilepsy itself was not found to be associated with the long-term child developmental outcome measure, confounding by indication seems less likely.

Other potential confounding factors which we considered were tonic-clonic seizures during pregnancy, periconceptional use of folic acid, alcohol and nicotine exposure during each trimester, breastfeeding, maternal age at delivery, maternal educational level, gestational age, gender, age at assessment, presence or absence of congenital malformations, and time of inclusion in the EURAP-NL database.

Potential confounders were examined for a relationship with medication and a relationship with the outcome measure. As expected, maternal IQ was found to be an important confounder for neurocognitive outcome measures. Likewise, maternal behavioral problems proved to be an important confounder in the analyses with child behavior.

Although alcohol and nicotine use during pregnancy were found to have no significant relationship with neurocognitive outcome measures, there was a significant difference between type of AED on these confounders: mothers who had used VPA were more likely to have used nicotine during each trimester, while mothers who had used LTG were more likely to have used alcohol during the first trimester. We were not able to find an explanation for these relationships between prescribed AEDs and the two social drugs. Further studies may help to confirm or refute the relationship, and if confirmed to explore the role of e.g. pharmacokinetic interactions or interactions between specific epilepsies and predispositions to social drug use. A study on the use of divalproex in smoking cessation previously found an unexpected association between divalproex and a greater craving and arousal level during smoking. Divalproex is a commonly used form of valproate. It is possible that mothers who used valproate, experienced more difficulty to stop with nicotine use during pregnancy, because of possible interactions between smoking and medication. This might explain the higher percentage of mothers using nicotine within the valproate group.

Mothers who used lamotrigine during pregnancy were more likely to have used alcohol during particularly the first trimester. Because of the possibility of unplanned pregnancies, we especially made a distinction between alcohol and nicotine exposure during the first trimester and during the second or third trimester, instead of examining the exposure during the entire pregnancy. According to information from the pregnancy registry, many women stopped using alcohol when they found out that
they were pregnant (at 6-8 weeks of pregnancy). The combination of oral contraceptive and lamotrigine does not pose a higher risk for unplanned pregnancy, as is known about the combination with enzyme inducing AEDs (such as phenytoin, phenobarbital, carbamazepine or oxcarbazepine)\textsuperscript{49}. Therefore, it remains unclear what is the cause of the association between lamotrigine and alcohol use during pregnancy as observed in the current study. It seems, nevertheless, important that women with epilepsy have to be well-informed of the risks and factors contributing to unintended pregnancies\textsuperscript{50}.

Frequent tonic-clonic seizures during pregnancy have previously been associated with reduced cognitive functions in the child\textsuperscript{51}. This has not been found in other studies\textsuperscript{11,13,14}. In our study there was no significant difference between mothers from the four AED groups regarding tonic-clonic seizures, and no associations were found between tonic-clonic seizures and outcome measures.

The use of folic acid during pregnancy is customary in the general population. For women with epilepsy it is also recommended, especially because of possible associations between folate metabolism and increased risks of neural tube defects in valproate exposure\textsuperscript{52,53}. However, there is controversy about the recommended dose for women with epilepsy, which varies from 0.4 to 5.0 mg/day\textsuperscript{54}. The mechanisms of periconceptional folic acid on prenatal development is not fully known, but positive associations have been found with higher intelligence scores in children of mothers with epilepsy\textsuperscript{11}. Recently an association with reduced risk of autistic traits was also reported in prenatally AED-exposed children of mothers with epilepsy\textsuperscript{55}. We did not find significant associations between periconceptional folic acid use and outcome measures. In our cohort, the majority of women had used folic acid (80-90%), this percentage was higher than in other prospective studies (e.g., NEAD study 40-60%)\textsuperscript{11}, and this may have reduced the power to detect a difference.

Breastfeeding in women with epilepsy is nowadays encouraged\textsuperscript{56} and positive associations between breastfeeding and cognitive and behavioral outcome measures have been reported\textsuperscript{57,58}. We found no significant association between breastfeeding and neurocognitive outcome measures. For behavioral outcome measures there were some significant associations, with breastfed children showing fewer behavioral problems. The proportion of breastfed children in our cohort was however rather small (16-28%). Over the years (2007-2011), a slight increase in breastfeeding was seen, but most women were advised not to breastfeed their children. Other studies examined children who were breastfed for at least six months\textsuperscript{57,58}. In our analysis we classified all children as breastfed when they...
had been nursed any time duration, varying from only a couple of postnatal days to more than six months. For mothers with epilepsy who wish to breastfeed, the benefits are usually considered to outweigh the risks. Providing accurate information about breastfeeding and AEDs to women with epilepsy is therefore recommended.

*Is there a role for antiepileptic drug dose?*

Teratogenic risks of AED have previously been found to be dose related. Especially VPA has shown a consistent dose-effect on a number of teratogenic endpoints, including major malformations and cognitive development. Although we did not find a significant relationship between VPA dose and cognition (intelligence) or behavioral outcomes, for some of the neurocognitive measures a significant dose relationship was found. Dose of CBZ, LTG or LEV were not found to be related with outcome measures. The relatively low dosages in our cohort, in combination with the small sample size of some AED exposure groups, may have influenced the high proportion of nonsignificant relationships with dose.

We used first trimester dose within our analyses, similar to the analyses of the EURAP pregnancy registry on malformations. As cognitive and behavioral development of the child also pertain to the third trimester, we also explored relationships with third trimester dose. We found similar with first trimester dose nonsignificant results. In particular, LTG dose was adjusted during pregnancy, with the dose being increased in most cases. It is known that LTG dose is often changed during pregnancy because of pregnancy induced changes in pharmacokinetics. We did, however, not have blood levels of pregnant women, so the daily dose may differ from the level to which the child has been exposed in utero.

*Is there a role for family factors?*

Besides the exposure to AEDs during pregnancy, children of mothers with epilepsy also have a mother with a chronic medical condition. Maternal epilepsy, its impact on the family system, and other family factors may contribute to child development as well. In Chapter 2 we reviewed the literature on possible associations between distinct family factors and developmental outcomes in prenatally AED-exposed children. We found that research on the role of family factors in children of women with epilepsy is rare. The few reported studies focused predominantly on stressors and demands in mothers with epilepsy, while less attention was given to resiliency factors pertaining to family
resources and strengths.

In Chapter 6 we examined whether mothers with epilepsy (n = 175) experienced family problems (e.g., parenting stress) and investigated the possible mediating role of distinct family factors in the relationship between maternal epilepsy and child behavioral problems. Following the social-ecological model of Bronfenbrenner\textsuperscript{66} and the transactional model of Belsky\textsuperscript{67}, we distinguished four types of family factors: proximal, distal, contextual and global family factors\textsuperscript{68}.

We found that mothers with epilepsy experienced significantly more parentings stress and problems with parenting compared to mothers from the general population. Compared to mothers from a clinical population of children with psychiatric problems they reported fewer problems. Previous studies on mothers with epilepsy reported also increased parenting stress, and showed that mothers with epilepsy had problems caring for themselves and for their child\textsuperscript{27,69,70}.

Impact of maternal epilepsy was significantly related to quality of parent-child interaction, parenting stress, parental psychopathology (measured as maternal behavioral problems) and family functioning. Impact of epilepsy was also significantly associated with internalizing problems, but not with externalizing problems. Family factors were significantly associated with child internalizing and externalizing problems. We found, with hierarchical multilevel analyses, that maternal epilepsy, global, contextual and distal family factors each had a significant contribution to child internalizing problems. Distal family factors (consisting of parental psychopathology and parenting stress) contributed most to internalizing problems and showed a mediating role for previous factors (namely family functioning, maternal educational level, family type, negative life events, and impact of epilepsy) in the model. Global, contextual, distal and proximal family factors were all found to be significant contributors to externalizing problems, with the factor most proximal to the child (quality of parent-child interaction) showing the largest effect.

Previous research on children of parents with a chronic medical condition reported increased behavioral problems, in particular internalizing problem behavior\textsuperscript{71}. In line with the theoretical expectations, based on the Family Systems-Illness model\textsuperscript{72} and the ABCX model of stress and adaptation\textsuperscript{73}, children of mothers with epilepsy seem to face stress as well, due to increased parenting stress and psychopathology in the mother, with mothers with more severe epilepsy also showing more psychiatric comorbidities. For children of mothers with epilepsy there are also specific epilepsy related factors that can play a role, worrying about the mother or experiencing an epileptic seizure can
be stressful or even traumatic for a child. In Box 1 we present, as an example, a case in which the impact of maternal epilepsy plays a role in the behavior of the child (see intermezzo, Box 1), as well as the potential importance of intervention. It shows what kind of influence it can have, on the parent-child relationship and the social-emotional development of a child, when a mother has active epilepsy. In most cases of developmental problems in the offspring, it is not so clear what the contributions of maternal epilepsy and the family perspective versus the exposure to antiepileptic drugs are. This example shows, however, how the impact of the maternal epilepsy can be on the child and the family and underlines the need to ask about family life. It also illustrates that psychological interventions can help children cope with the chronic medical condition of their mother or decrease their behavioral problems.

In chapter 7 we showed that the group of mothers that participated in our study (n = 156) generally fared well, with well-controlled seizures. Nevertheless, epilepsy negatively impacted the lives of some mothers. A quarter of the mothers reported internalizing problems within the borderline or clinical range. Behavioral problems were significantly associated with lower quality of life, higher epilepsy severity, and greater impact of epilepsy. Impact of epilepsy mostly affected self-confidence, work and general health of mothers. Regression analyses showed that epilepsy severity and quality of life contributed most to impact of epilepsy, while other factors (maternal education, family type, behavioral problems and parenting stress) were found to be nonsignificant contributors.

For clinicians who work with women with epilepsy, it is important to pay attention to the family and psychosocial factors that are involved in living with epilepsy. There are various interventions specifically for people with epilepsy which may improve the quality of life. For mothers with epilepsy, specific interventions that reduce parenting stress and improve the quality of parent-child interaction are also recommended (e.g., mindful parenting).
Box 1: Example of impact of maternal epilepsy on child behavior

Z is a female child, born 2007, in utero exposed to lamotrigine (550 mg/day), with a healthy development and average intelligence (FSIQ 92). She was seen within the study at seven and nine years old and followed until eleven. Her mother has localization-related epilepsy with complex partial seizures, several times per week. After a long trajectory (of hospitalization and recovery) mother has had epilepsy surgery in 2016/2017 and became seizure free since. The child has separation anxiety, presumably caused by traumatic experiences around epileptic seizures of her mother.

During seizures, mother is partially unconscious. She does not fall and can move, but is not aware of her actions. Her daughter is terrified that something may happen to her mother and doesn’t dare to leave her alone, possibly due to traumatic experiences. Once the mother had a seizure while waiting at a traffic light. Her daughter, at the age of five years, had to prevent her mother from crossing the road despite the red light. For years, mother had to leave her child crying at school every day. Without her mother, she could not play with other children or sleep alone. At the age of ten years old, she still had extreme separation anxiety, which negatively affected her daily life. When mother became seizure free, trauma treatment had started and Z was hoping that she would be able to overcome her fears.

At the end of 2018 Z successfully completed the trauma treatment WRITEjunior, which was combined with parts of the cognitive behavioral therapy for anxiety (Discussing+Doing=Daring (DDD)\(^{78}\)). Her mother also followed a mindful parenting course. Between pre- and posttest scores on the Children’s Responses to Trauma Inventory\(^{79}\) (CRTI; Schokverwerkingsvragenlijst: minimum score 34, maximum score 170), there was a decline in symptoms of posttraumatic stress from clinical range (total score 108 pretest) to non-clinical (total score 37 posttest).

It is, altogether, important, when examining children of mothers with epilepsy, to consider various factors: the type of prenatal AED exposure, with each AED showing to have its own long-term teratogenic profile on neurocognitive and behavioral development, wherein dose probably plays a role for some AED, such as with VPA. Pregnancy-related factors, including alcohol and nicotine exposure, as well as risk factors concerning delivery, should be incorporated. In addition, environmental factors, social economic status, upbringing and severity of mother’s epilepsy contribute to the child. These factors together and in interaction form the child and influence development and must be examined when a child encounters problems.

Strengths and limitations

This thesis has a number of strengths and limitations. An important strength of this empirical study is the extensive diagnostic screening of children of mothers with epilepsy, with multi methods and multi informants, including a comprehensive child assessment with assessors blinded for AED exposure type. We used standardized tests and questionnaires, and assessors (child (neuro)psychologists) were trained and supervised using a test-protocol. Prenatally AED exposed children were examined for different domains of development, with neurocognitive and behavioral functioning, and the contribution of distinct family factors. The study is based on an empirical and theoretical basis, incorporating the interplay between maternal epilepsy, prenatal AED exposure and social-ecological
factors, from the idea that a child reciprocally relates to its environment. This research contributed to more knowledge about the long-term effects of prenatal exposure to AED, including the increasingly used newer AEDs: lamotrigine and levetiracetam.

Another strength of this study is the observational design, with the collaboration with the European Registry of Antiepileptic Drugs and Pregnancy (EURAP-NL) database, in which pregnancy and maternal health information was collected prospectively. Potential confounders have been extensively investigated and included maternal IQ and maternal behavioral problems. Mother and fathers were invited to participate in the study and we included children from across the Netherlands.

On the other hand, pregnancy registers reach only part of the women with epilepsy and this may limit the extrapolation of data to the general population. In addition, our inclusion rate was lower than we had anticipated (around 40% instead of 50%). Re-contacting families who did not respond to letters by phone, increased our inclusion somewhat, but was limited by current high rates of changes of telephone numbers. We also included brothers and sisters from the same family (26 of 181 children). This may have caused dependency, but we controlled for this with multilevel analyses. For neurocognitive outcome measures we also performed analyses with only one child from each family (the first-born within the study), with similar results. That the number of children among the different exposure groups is unevenly distributed was inevitable, within this cohort more children were exposed to LTG than to the other AED.

Generalization of study results may also be limited due to the relatively high educational level of mothers: more than half of the mothers received higher education. It is known that Social Economic Status (SES) is associated with child development. Educational level of the parents seems particularly associated with child cognitive functioning, we therefore used maternal educational level as proxy for SES. Children from lower SES backgrounds have fewer opportunities in life. For example, preterm children from different SES backgrounds had differential developmental pathways despite shared difficulties at birth. SES may similarly be associated with outcomes in children who have been exposed to AEDs in utero. Because in our study educational level significantly differed between participating and nonparticipating families, associations between lower SES and child neurocognitive functions might therefore not have been detected. Future studies should therefore put their best efforts in equal recruitment of families from all SES backgrounds.

We measured epilepsy severity as a composite variable based on seizure type, seizure
frequency and number of AEDs used\textsuperscript{80,81}. It is, however, arguable whether this gives a reliable representation of epilepsy severity in the context of this study of child development. It considers a tonic-clonic seizure as more severe than absences. If a mother has prolonged periods of absences, for example throughout the day, this can have an enormous impact on life, though. This is not incorporated in the rating. Combinations of type of seizures are also not accounted for in this rating system, where we scored the seizure with the highest severity level. Additional analyses with the three separate components showed that seizure frequency had the largest impact on child behavior, but the overall results remained similar. We also used a subjective measure on impact of maternal epilepsy to investigate the experienced burden of epilepsy. This gave us information on which aspects of her (family) life the mother felt the greatest impact.

**Recommendations for future research**

Based on our findings it seems important to follow prenatally AED exposed children over time. Although the six-or seven-year-old is at a reliable age to measure neurocognitive functions, children are still developing and a lot can change: developmental problems can decrease, increase or remain the same. With longer follow-up, additional dependent and independent factors may also influence development. It has been suggested that prenatal AED exposure is associated with a transient developmental delay and that children might get fewer problems with aging. However, a recent study on people diagnosed with fetal valproate syndrome, showed that problems still existed into adulthood\textsuperscript{33}. More studies are needed, also on less severe cases of VPA exposure and other AEDs. Repeating of measures between eight and ten years old is therefore one of the recommendations, followed by a measurement around twelve years of age, when children are in the transition from primary school to secondary high school and enter the teenage years. It is also interesting to follow children from adolescence to young adults, for example with respect to the effect of prenatal exposures on puberty and hormonal changes, and into adulthood in order to evaluate, amongst others, reproductive fitness and third generation outcome. At the age of twelve and beyond it is possible to examine more in depth how cognitive differences may have an impact on school functioning and later employment. A Danish population register study of 2018 showed an association between prenatal VPA exposure and lower school performances at twelve years of age\textsuperscript{18}. Children who were not able to complete the national tests were however not included in this study, so results may be biased towards better academic functioning children. With a population-based prospective
observational design it is possible to include those that drop out of regular school and to control for maternal and, as far as feasible, paternal IQ.

Monitoring children from an earlier age onwards is also recommended. This will probably increase inclusion in follow-up studies, with earlier detection of signs of developmental delay and more precise attribution to preceding risk factors. This may also reduce potential selection bias of children who exhibit problems at an early age and are missed out in older cohorts as they are already seen within regular youth care. Specific attention can be given to the early development and mother-child interaction after birth to follow the wellbeing of the mother with epilepsy as well as to provide targeted help with any (psychological) problems. In chapter 7 we showed that little is known about motherhood in women with epilepsy, while mothers do seem to have problems with parenting and caring for themselves. Qualitative research into motherhood with epilepsy, both into newborn mothers and mothers with school-age children, can be an interesting addition to gain insight into certain problems mothers with epilepsy encounter. How do they manage sleep deprivation, breastfeeding and parenting stress when having epilepsy? This information can subsequently be used to prepare expectant mothers with epilepsy.

Inclusion of children at younger age will help to increase the denominators with less selective ascertainment, increase the statistical power, and provide more opportunities for less biased longer-term follow-up studies. In our study, some AED-exposed groups were small, requiring replication of results. Cooperation with other countries such as within the EURAP/NCEP study is of great importance, as this increases the numbers needed to detect and estimate developmental risks at an earlier stage. Also new AEDs should be considered for immediate inclusion into these post-marketing surveillance studies upon release to the market. As long as not all patients with epilepsy are seizure free and without side effects on currently available AEDs, new AEDs will still be developed and introduced into the market. The question of the teratogenic risks of the use of these medications during pregnancy will remain highly relevant!

Our research focused on the comparison between four AED monotherapies, but it is important to also examine specific polytherapy combinations, as there is a demand in clinical practice for this information. Earlier research on congenital malformations showed that with a low dose of VPA in combination with LTG the risks of birth defects were lower than with a higher dose of monotherapy VPA. For long-term developmental outcomes, however, little is known about specific polytherapy
Pregnancy registries have a leading function and should be encouraged to include as many pregnancies as possible. Specific attention must be given to include also women with a lower social economic status, and women with epilepsy who do not use AEDs during pregnancy. Non-exposed children of mothers with epilepsy can then function as an additional control group to children who are prenatally exposed to AED, although even such a comparison group doesn't solve the problem of confounding by indication completely. Inclusion of all pregnancies, for example also those exposed for other maternal indications like migraine, pain or mood disorders, will increase power, promote earlier detection of risks, and provide additional means to control for confounding by indication.

Despite all this research, we are still not able to predict, after prenatal exposure to AEDs, the normal or abnormal outcome of pregnancy in general and development in particular. More research is needed to gain knowledge about the susceptibility of children: why do some children experience problems and others not? Genetics can play an important role in this. A number of categories of genetic factors can be considered, namely the genetics of epilepsy and variable expression (epilepsy in the mother or other family members and other symptoms in the child), genetics unrelated to maternal epilepsy (maternal, paternal and genetics of the child), and possible interactions between genetic factors and AED (e.g., pharmacokinetics and pharmacodynamics) resulting in genetic susceptibility to teratogenic side effects.

In view of the considerably larger progress in identification of genetic causes of major malformations as a dichotomous outcome versus the various aspects of development as a continuous outcome variable, it is likely that a search for genes that predispose to teratogenic side effects will have a greater chance of success when primarily focused on major malformations\textsuperscript{37,39}. On a behavioral level it is far more complicated to identify specific genetic causes, as it involves several genes and possible interactions, prenatally as well as during postnatal life\textsuperscript{85}. Best possible approach may focus on major malformations after VPA (high number of exposures, high risk, dose effects) as well as teratogenic effects where the putative molecular biological mechanism is known from experimental studies.

It is clear that multiple factors are involved in the development of children of mothers with epilepsy. This makes that developmental teratology in human is complex, where cause and effect cannot always be distinguished. To further illustrate this complexity, we present two children who
have been exposed to VPA during pregnancy. They were extensively studied within a clinical setting elsewhere, because of developmental, behavioral and learning problems. Parents provided the reports and gave permission to use this information for an anonymous short case description (intermezzo, Box 2). These two case descriptions of prenatal VPA exposed children show that multiple causative factors (prenatal exposure, birth complications, environmental factors, such as life events, family and school, and genetic factors independent from or linked to maternal epilepsy), and their interactions have to be taken into account when examining the developmental outcome of offspring of mothers with epilepsy on medication during pregnancy. An important question that future researchers should address is how they can examine this complexity on a group level. Case studies may provide valuable information to gain more insight into the various factors involved, and raise specific hypotheses that can be tested.

A specific method which may help to distinguish teratotogenic effects from genetic factors may be offered by 3D analysis of facial morphology. By examining the facial features of both parents and the child, genetic factors may be differentiated from teratogenic factors. Such analysis with e.g. prenatally VPA-exposed children and their parents (‘trio-3D’) can lead to a better delineation of fetal valproate syndrome and the broader spectrum of developmental teratogenicity of VPA. This will also offer new possibilities to investigate associations between dysmorphic facial features and cognitive functioning.
Summary and discussion

Box 2: Case descriptions of prenatal valproate exposure

Child X is a male, born in 2007, prenatally exposed to 1,000 mg/day of valproate during the first trimester and 1,500 mg/day during the second and third trimester on indication of maternal generalized tonic-clonic epilepsy. After a normal pregnancy, without seizures, X was born after 41 weeks of pregnancy, with a birth weight of 3,480 grams. At birth, the umbilical cord was entangled around his neck, after which he received oxygen. Apgar scores were 6, 8 and 10, after respectively one, five and ten minutes. A short lingual frenulum (ICD-10: Q38.1), leading to feeding problems, was surgically cut after the first week. Based on clinical genetic examination at the age of three months, there were no physical features of fetal valproate syndrome. When X grew older, his development was delayed, especially in language and social development. Around his third birthday he was seen at the audiological center for hearing, speech and language. He appeared to have a language deficiency, where after speech therapy was started. At four years of age he was referred to a psychiatrist because of autism characteristics. At seven years of age he underwent again a psychological examination and was diagnosed with PDD-NOS. Intelligence testing (WISC-III-NL) revealed a disharmonic profile, with verbal intelligence on below average level (VIQ 86) and performance intelligence on average level (PIQ 102). A repeat of intelligence test at ten years of age showed a similar profile (VIQ 81; PIQ 96). X attends special education (cluster 4). His parents are divorced. Both parents have received a higher education. Over the years, X and his parents have had much psychological help and support with his development, behavior and learning. DNA analysis by ‘array’ at nine years of age showed a normal male profile. The geneticist had concluded that the cause of developmental and behavioral problems is most likely multifactorial with genetic and non-genetic factors (environmental), and possible interactions with valproate exposure.

Child Y is a male, born in 2009, prenatally exposed to 900 mg/day of valproate. He grows up in an intact family with three children. Y is the oldest, the younger children have also been exposed to valproate, but show less or no problems. Parents have a lower educational level. His mother has epilepsy with generalized tonic-clonic seizures. Mother smoked one cigarette per day during pregnancy. After a normal pregnancy Y was born after 38 weeks, with a birth weight of 2,795 grams, and Apgar scores 8 and 9. Y had no congenital malformations. From the neonatal period onwards, he suffered from chronic cough, requiring long-term antibiotics. Y was often sick. As baby he used to cry excessively. At the age of four months, a reflux was discovered. There was a preferred posture with plagiocephaly, which was treated with manipulation of the neck vertebrae, a helmet and physiotherapy. Y showed a delay in psychomotor and language development. At the age of six he was referred to a rehabilitation hospital due to a suspicion of a developmental coordination disorder (DCD). Psychomotor examination showed, however, insufficient indications for a diagnosis. Due to maternal valproate use during pregnancy, fetal valproate syndrome was also considered. Y had problems at school, he repeated a year (class 3), and the question was whether he could stay on a regular school. On intelligence test (WISC-III-NL) he performed below average (FSIQ 87), with a harmonic profile (VIQ 90; PIQ 88). He showed a high level of aspiration and fear of failure, which seemed to hinder his overall functioning. Y has problems with attention, but there was no indication for a diagnosis of ADHD. Clinical symptoms of autistic behavior were reported by parents and the teacher. At the age of seven, Y was referred for a clinical genetic examination. DNA analysis by ‘microarray’ revealed a normal male profile (XY,46). Y showed some features of fetal valproate syndrome, but the geneticist had concluded that the cause of the syndrome cannot be attributed to valproate with certainty. Multiple other factors can be involved like genetic predisposition, and environmental factors such as family and school.

The research into children of mothers with epilepsy could be embedded in the regular care for women with epilepsy. Cooperation can also be sought through a multicenter approach including centers that treat women of childbearing age with AEDs because of epilepsy as well as other disorders. More in general, it is important that teratology pays more attention to long-term effects.
Recommendations for clinical practice

As mentioned above, research on children of mothers with epilepsy can go hand in hand with clinical practice. Dissemination of knowledge is an important goal of clinical research, among clinicians (e.g., neurologists, nursing specialists, gynecologists, psychologists) and women with epilepsy themselves. A recent survey study from German speaking countries showed that more attention should be given to information provision: 41% of women taking VPA were found to be unaware of the teratogenic risks. The newspaper reports in the Netherlands and neighboring countries also suggest that the knowledge about the teratogenic risks of VPA are not yet spread to a broader public. A national center of expertise that offers information for women with epilepsy and guides these women during pregnancy could be of help. Care pathways for pregnancy and epilepsy within the epilepsy centers and their network of outpatient clinics could be further extended and join with an information point on children of mothers with epilepsy. The Teratogen Information Service (TIS) of the Netherlands Pharmacovigilance Center Lareb can help with informational support to physicians in charge of pregnancy care.

The information obtained from this thesis can be used to inform women with epilepsy, both for women with a child wish, pregnant women and those who already have children (see for management of women with epilepsy Box 3). Specific attention can be given to the wellbeing of the mother with epilepsy and family factors involved. If a mother currently is concerned about her child, there should be a low threshold for access to a dedicated physician at the peripheral or academic hospital, or specific third-line epilepsy center, and, if needed, referral to a (neuro)psychologist or clinical geneticist for further diagnostic screening. Given results provided in this thesis, VPA-exposed children as well as children exposed to other AED, should be screened on behavioral problems also from a family perspective. Psychologists, speech therapists and physiotherapists are in addition advised to monitor language and motor development of VPA-exposed children as early interventions can reduce or prevent problems later in life. For children prenatally exposed to LTG or LEV, attention may be paid to a possible disharmonic intelligence profile, in favor of verbal functioning, which can be expressed in both school performances as in behavioral problems. Psychologists who work with children of mothers with epilepsy need to pay attention as well to the aspects of having a mother with a chronic medical condition. A child may be worried about the mother, or experience fear of becoming ill themselves. Psychoeducation for these children is therefore recommended. In conclusion, it is worth
to consider the extend the foreseen center(s) of expertise for women with epilepsy, child wish and pregnancy also with diagnostic and therapeutic expertise in the field of child development. Based on the specific results of the current study, the identification of behavioral problems can also offer starting points for interventions. Interventions for children with internalizing behavioral problems can focus on the impact of the mother with epilepsy, reducing parental behavioral problems and parenting stress as mediating factor for the problem behavior of the child. In externalizing behavioral problems, interventions can target on increasing a positive parent-child interaction. From a biopsychosocial perspective, it is thereby essential to take into account multiple factors that may be a risk or protective factor for the development of the child (see also Box 4).

**Box 3. Management of women with epilepsy at different stages**

<table>
<thead>
<tr>
<th>Women with epilepsy with a child wish</th>
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<tbody>
<tr>
<td>Weigh the risks to the mother and to the unborn child.</td>
</tr>
<tr>
<td>Reevaluate AED type and indication, and restrict to monotherapy, whenever possible.</td>
</tr>
<tr>
<td>Avoid valproate, whenever possible.</td>
</tr>
<tr>
<td>Establish the lowest effective dose regardless of AED type.</td>
</tr>
<tr>
<td>Provide information on epilepsy and pregnancy, including teratogenic risks of congenital malformations as well as possible long-term effects.</td>
</tr>
<tr>
<td>Consider preconception folic acid supplementation (routinely 0.4-0.5 mg/day; 4.0-5.0 mg/day only at specific other indications like clinical or biochemical evidence of folic acid deficiency).</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Women with epilepsy during pregnancy</th>
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</thead>
<tbody>
<tr>
<td>Avoidance of known seizure provoking factors.</td>
</tr>
<tr>
<td>Serum drug level monitoring, especially of lamotrigine, to maintain seizure control.</td>
</tr>
<tr>
<td>Caution with AED switch or withdrawal.</td>
</tr>
<tr>
<td>Discuss options for prenatal diagnostics.</td>
</tr>
<tr>
<td>Prepare for delivery and provide information on possible obstetric complications.</td>
</tr>
<tr>
<td>Give information on having a child, while living with epilepsy.</td>
</tr>
<tr>
<td>Evaluate wellbeing of the mother and perceptions about caring for the child.</td>
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<table>
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<tr>
<th>Women with epilepsy after pregnancy</th>
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</thead>
<tbody>
<tr>
<td>Monitor mother and infant after delivery and adjust when necessary AED dose.</td>
</tr>
<tr>
<td>Encourage breastfeeding, but with monitoring of baby’s wellbeing.</td>
</tr>
<tr>
<td>Provide help and support for the new-born mother to prevent relapse of seizure.</td>
</tr>
<tr>
<td>Help to prevent lack of sleep and possible postpartum depression.</td>
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<table>
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<tr>
<th>Women with epilepsy and their offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routinely ask about the wellbeing of the mother and provide support with psychological or social problems, including parenting.</td>
</tr>
<tr>
<td>Screen prenatal AED exposed children for possible developmental delay or behavioral problems.</td>
</tr>
<tr>
<td>Provide children with psycho-education on having a mother with a chronic condition, especially when the mother has active epilepsy.</td>
</tr>
</tbody>
</table>

*Based on currently available guidelines and results of this thesis. An individual approach that is personalized to each woman with epilepsy is essential, with a multidisciplinary team, including neurologists, nursing specialists, gynecologists, psychologists and other health care professionals.*

For clinicians working with women with epilepsy it is thus of importance to look beyond the medical side of the chronic condition. Seizure control is important, but attention for the psychosocial...
factors involved with epilepsy, as well as the role of the partner, family and children is important as well. Questions about the welfare of the mother and her children should therefore be part of annual appointments.

Box 4. Specific risk and protective factors in children of mothers with epilepsy which may provide targets for interventions.

<table>
<thead>
<tr>
<th>Parental psychopathology</th>
<th>Family functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenting stress</td>
<td>Positive parent-child relationship quality</td>
</tr>
<tr>
<td>High epilepsy severity</td>
<td>Low epilepsy severity</td>
</tr>
<tr>
<td>Low social economic status</td>
<td>High social economic status</td>
</tr>
<tr>
<td>Child behavioral problems</td>
<td>Partner support and social network</td>
</tr>
<tr>
<td>Developmental delay / cognitive deficits</td>
<td>Child characteristics / easy temperament</td>
</tr>
</tbody>
</table>

Interventions can focus on reducing risk factors and strengthening protective factors, at child, parent and family level. This will provide a balance between different development tasks and skills which benefits the long-term outcome of the child.

This thesis started with a case description within a Dutch newspaper on VPA use during pregnancy, in which a mother wondered: Have I poisoned my child? This is an expression of the guilt feeling experienced by many women with epilepsy who have a child with a malformation, intellectual disability or behavioral problem attributed to having taken AED medication during pregnancy. It may also lead to questions about how the abnormal outcome could have been avoided. Was all information available, provided and its understanding checked? Were options discussed? With what certainty can the observed abnormalities be attributed to the prescribed AEDs? These are questions that preferably are addressed in discussion with the physician, but, unfortunately, sometimes even end up in court.

The treatment and guidance of women with epilepsy involves several dilemma’s and considerations on balancing the risks between mother and child, given the information available at the time. Only after lower intelligence and increased risks of autism in prenatally VPA-exposed children were reported in 2013, the European Medicines Agency (EMA) issued a first warning on the use of VPA during pregnancy. Only in the beginning of 2018 the EMA officially issued a guideline to avoid VPA in girls and women of childbearing age, whenever possible, whereas other teratogenic risks of
VPA became known many decades before. A gradual decrease in the use of VPA in pregnant women with epilepsy had already been observed for years\textsuperscript{104,105}, although it is difficult to estimate to what extent knowledge about teratogenic effects contributed to this trend, given multiple other factors like new AEDs becoming available, marketing strategies, professional traditions, insurance policies etc.

Women with epilepsy who need AEDs during pregnancy deserve to be well-informed, whereby the risks for the mother (risks of seizures, morbidity) and the risks of the child (congenital malformations, cognitive deficits, behavioral problems) are carefully weighed in a personal discussion between patient and physician. Despite the fact that we identified some risk factors for neurocognitive and behavioral development, it is reassuring that most children of mothers with epilepsy and on medication are born healthy and develop normally.

This thesis has shown that developmental teratogenicity is a complex whole, wherein many factors play a role. A next step was taken to gain more knowledge on developmental teratogenic risks of AED, including LTG and LEV, and the contribution of distinct family factors, in order to help mothers with epilepsy, their children and families, to ultimately improve their quality of life.

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