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The transition from pediatric to adult care for youth with epilepsy: Basic biological, sociological, and psychological issues

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ABSTRACT

Transition from pediatric to adult health care for adolescents with epilepsy is challenging for the patient, family, and health care workers. This paper is the first of three that summarize the main findings from the 2nd Symposium on Transition in Epilepsies, held in Paris from June 14–25, 2016. In this paper we describe five basic themes that have an important effect on transition. First, there are important brain changes in adolescence that leave an imbalance between risk taking and pleasure seeking behaviors and frontal executive function compared with adults. Second, puberty is a major change during the transition age. The three most important but separate neuroendocrine axes involved in puberty are gonadarche (activation of the gonads), adrenarche (activation of adrenal androgen production), and activation of the growth hormone-insulin like growth factor. Third, sexual debut occurs during the transition years, and at an earlier age in adolescents with epilepsy than controls. Adult sexual performance is often unsatisfactory. Although AED-induced alterations in sexual hormones and temporal lobe epilepsy may play a role in hyposexuality, depression, anxiety, and other social factors appear most important. Fourth, psychological development is very important with an evolution from an early stage (ages 10–13 years) with concrete thinking, to a middle stage (ages 14–17) with analytic and more abstract introspective thinking, and then to a late stage (ages 18–21) with at least the beginnings of adult reasoning. Epilepsy may derail this relatively orderly progression. Adolescents with autistic spectrum disorder may present with severe behavior problems that are sometimes related to undiagnosed epilepsy. Fifth, bone health in adolescence is critical to establish adequate mineralization for all of adult life. While AED interference with Vitamin D metabolism is important, there is evidence that the effects of AEDs on bone are more complex and involve changes in remodeling. Hence, some non-inducing AEDs may have a significant effect on bone health. All five of these themes lead to recommendations for how to approach adolescents and young adults during transition and some specific interventions to achieve maximum long-term adult independence and quality of life.

1. The transition from pediatric to adult care for youth with epilepsy

As adolescents age, they nearly always move from pediatric to adult care. For adolescents with any chronic disease, this transition may be difficult or unsatisfactory; however, there are special reasons for concern for transition for adolescents with epilepsy. Many pediatric-onset epilepsy syndromes have different treatments and different adult outcomes with cognitive and other co-morbidities making the process of transition especially challenging. We suspect that many adult epilepsy care providers are intimidated by the complexity of pediatric epilepsies that may differ considerably from the typical adult with focal epilepsy of temporal lobe origin.

The process of transition begins in childhood and has the goal of helping children to become as independent as possible as adults with the best possible seizure control. The terms transition and transfer are often used interchangeably, but transition is a longitudinal education process, while transfer is the simpler act of formally passing care from pediatric to adult health care providers. The process of transition ideally begins in early adolescence and may continue even after transfer to adult care. Thus "transition age" ranges from about 13 to 19 years of age.

In June 2016, we participated in a two-day closed meeting about transition for children with epilepsy that included about 30 pediatric and adult neurologists/epileptologists from several European countries including France, Italy, and Britain as well as the United States and

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Canada. The structure of this meeting involved a series of 30 prepared presentations and extensive discussion. Nearly all authors provided an abstract of their presentation and their slides. This meeting was the second symposium on transition in epilepsies in this setting. The first meeting occurred in 2013 and was summarized by a journal supplement [1].

This paper and two subsequent papers published in Epilepsy & Behavior will summarize the presentations and discussion with the goal of clarifying the types of problems encountered in transition from pediatric and adult epilepsy care perspectives. The current paper focuses on the brain, endocrine, psychological, and sociological changes that occur around the time of transition both in "normal" adolescents and adolescents with epilepsy. As well, we discuss the evolution of bone health with epilepsy treatment. The second paper considers issues related to the adult outcome of childhood epilepsy, and the final paper considers changes in treatment as the child ages to become an adult. Our goal is to increase awareness of transition issues for a variety of children with epilepsy and to assist all physicians caring for these young people to anticipate and deal with transition and maturational changes.

2. Changes in the brain through adolescence and childhood

A large literature has documented in great detail the normal brain changes through adolescence. Here we summarize some of the highlights but acknowledge that there is still more to learn (Table 1).

Adolescence is a time of tremendous refinement in brain development including changes in cerebral blood flow, grey matter density, white matter connectivity, and neurotransmitters [2]. The net effect of these changes is to create a transient imbalance between the impulsive and risk taking behavior of youth and the more sober risk assessment of an older person. Limbic structures mature more rapidly than prefrontal and frontal cortex [3]. The importance of this imbalance is that prefrontal cortex plays a major role in "executive function", which includes functions such as attention, decision making, and inhibitory control, regulation of emotion, organization, and long-range planning [4]. All of these factors have a major impact on the ability of adolescents to deal with the responsibility for their own health and the adult health care system [5].

2.1. Grey matter

In a longitudinal study of 13 healthy children with MRI studies every two years for 8–10 years, Gogtay et al. noted that grey matter becomes less dense between childhood and young adulthood with these changes starting in the posterior cortex and gradually moving to the frontal cortex and ending with the prefrontal cortex [6]. Decreasing grey matter density was postulated to be the result of synaptic pruning, increased myelination, and increasing axonal diameter.

Table 1
Key changes in the brain through childhood and adolescence.

- Grey matter loses density moving from occipital to frontal as the result of synaptic pruning, increased myelination, and increasing axonal diameter.
- White matter connectivity changes in many brain regions with greater connectivity to the frontal cortex.
- White matter fiber density, axonal diameter, and myelination show a "U"--shaped relationship with age – less in childhood, greater in adolescence in early adulthood, and less in later adulthood.
- Global cerebral blood flow increases in late childhood, plateaus in adolescence, and decreases in adulthood.
- Different brain areas are activated on fMRI in adolescents and adults with tasks that involve visual recognition of emotion.
- Dopamine, "the neurotransmitter for pleasure", increases in adolescence.
- The "reward pathway" has less input from frontal cortex in adolescents than adulthood suggesting that emotions and pleasure seeking are less inhibited.

2.2. White matter connectivity

A large cross-sectional study of 439 people between ages 12 and 30 years used 4-Tesla MRI to estimate changes in white matter connectivity with maturation [7]. The technique involved tractography and calculation of nodes of interaction. Changes in nodal activity were compared between adolescence and young adulthood. Many parts of the brain showed both increasing and decreasing connectivity over time but for the purpose of this discussion, we emphasize that there was a notable increase in the connectivity between nodes of activity in the frontal and prefrontal cortex and other brain structures.

Another MRI study of 119 right-handed individuals included 42 children and adolescents (ages 7–18 years) and 77 adults (19–68 years). This study investigated diffusion tensor tractography with a 3T machine and considered the change in fractional anisotrophy in many of the white matter tracts in the brain [8]. Fractional anisotrophy reflects white matter fiber density, axonal diameter, and myelination. For all tracts studied there was a U-shaped relationship of fractional anisotrophy with age, increasing from early childhood to about age 30 years and then decreasing with the greatest changes between age 15 and 25, the ages of transition. The U-shaped curve for the arcuate fasciculus was particularly striking. This structure plays an important role in connections between the frontal cortex and the rest of the brain.

Coupled with changes in grey and white matter, changes also occur in cerebral blood flow [9]. Positron emission tomography studies show an increase in brain metabolism as reflected by cerebral blood flow that increases through early childhood to a maximum at about age 8 years, then plateaus through adolescence and decreases in adulthood [10]. Functional MRI studies also show important changes between adolescents and adults. For example, in one experiment adolescents and adults were shown a picture of a frightened face [11]. All the adults studied correctly identified the emotion portrayed in the picture and their fMRIs showed marked activation in the frontal cortex. Only ~50% of adolescents recognized the emotion expressed by the picture and even fewer showed frontal cortex activation. This emotion recognition pattern has a major impact on social interaction and decision making in adolescence and emphasizes the major brain maturational changes that occur during the transition age.

2.3. Brain neurotransmitters and the reward pathway

There are large shifts in neurotransmitters through maturation. One of the most critical changes in adolescence is an increase in brain dopamine, particularly in the "reward" pathway that involves the ventral tegmental area, the nucleus accumbens (NA), and connections through the limbic system and eventually the frontal cortex [3,4,12]. At the time of puberty there is a major increase in brain dopamine with dopamine receptor density highest in the nucleus accumbens during adolescence. It is postulated that the nucleus accumbens and its connections play a key role in pleasure seeking behavior. In a famous experiment using a "Skinner Box", stimulating electrodes were inserted in the nucleus accumbens in rats with stimulation dependent on the rat pushing a lever [3]. Rats would push the lever and activate the stimulus for hours to the exclusion of feeding and drinking behavior. Inhibitory control of the nucleus accumbens, reward circuit, and amygdala appears to come from the prefrontal cortex via a complex balance between inhibition and excitation that is dependent on dopamine connections. However, the nucleus accumbens and limbic circuits appear to mature earlier than the prefrontal cortex, leaving the adolescent prone to relatively uninhibited, reward seeking, and sometimes risky behavior.

Summarizing this material, Casey and others have proposed that in early puberty there is a large increase in axons and synapses, followed by rapid pruning in later adolescence [3]. Pruning throughout adolescence is more prolonged in the prefrontal cortex versus the nucleus accumbens suggesting that the accumbens matures earlier than the prefrontal cortex. This creates a situation in adolescence when the "pleasure center" is

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mature but not well-connected to the prefrontal cortex. The net effect is that "in emotionally salient situations, the more mature limbic system wins over the prefrontal control system. When a poor decision is made in an emotional context, the adolescent knows better, but the emotional context biases his/her behavior in opposite direction of the sensible action".

Understanding this imbalance is important for physicians who care for children with epilepsy through the transition period [3,4]. Risk taking behavior is to be expected which may affect medication compliance or potentially dangerous combinations such as sleep deprivation plus excessive alcohol intake leading to poor seizure control. Importantly, there are interventions that can improve this situation, many of which are outlined in the third paper in this series.

3. Endocrinological changes in adolescence

The emergence of puberty in early adolescence has a striking influence on health and behavior. Pubertal onset is clinically defined by Tanner stage 2 that corresponds, in girls, to the initiation of breast development, and in boys, to the enlargement of the testes (volume >3 ml or testicular length ≥25 mm). The time of onset of puberty varies among ethnic groups, but in most populations the first signs of puberty appear around 10 years for girls and 12 years for boys [13]. During puberty, the maturation of the gonads leads to a functional reproductive system that corresponds to first menses in girls, and spermarche (the onset of sperm emission) in boys. Menarche occurs around two years after breast buds. Nevertheless, some endocrine maturational processes, such as bone maturation, still continue after the end of puberty.

The three most important but separate neuroendocrine axes involved in puberty are the hypothalamic–pituitary–gonadal axis leading to gonadarche (activation of the gonads), the hypothalamic–pituitary–adrenal axis, leading to adrenarche (activation of adrenal androgen production), and activation of the growth hormone-insulin like growth factor axis (GH-IGF). Estradiol also contributes to the pubertal peak of bone mineralization.

Gonadarche results from the activation of the hypothalamic–pituitary–gonadal axis. The mechanisms underlying this activation are partly understood. About two years before the beginning of clinical signs of puberty, nocturnal pulsatile secretion of gonadotropin-releasing hormone (GnRH) is initiated from hypothalamic GnRH neurons, leading to pulsatile secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior-hypophysis [14]. The increasing frequency of LH secretion stimulates the gonads and sexual steroid secretion (estradiol or testosterone). Luteinizing hormone and FSH also promote follicular maturation, ovulation, and gametogenesis. The timing of puberty onset is controlled by a complex interplay from stimulatory (leptin, glutamate, serotonin, galanine, dopamine, norepinephrine) or inhibitory (neuropeptin Y, melatonin, GABA) factors. The activation of GnRH neurons is thought to involve kisspeptin, a neuropeptide that signals via the Gαq-coupled receptor GPR54, located on GnRH neurons [15,16]. There are also influences from genetic, environmental, and nutritional factors.

Adrenarche is the maturation of adrenal glands and starts about two years before gonadarche [17] leading to a gradual increase in production of adrenal androgens dehydroepiandrosterone (DHEA) and DHEA-sulphate (DHEA-S) and secondarily to adrenal delta4-androstenedione. These androgens have a role in the development of androgen-dependent hair (axillary and pubic hair). Pubic hair development, also named pubarche, is due to peripheral conversion of DHEA-S to testosterone and then to dihydro-testosterone (the active form of testosterone) in most children of either sex. Local production of these androgens also stimulates the development of apocrine glands within the skin, which can lead to body odor. Conversion of DHEA to active androgens within sebaceous glands can also lead to acne in some children. Dehydroepiandrosterone and DHEA-S may play an important role in brain maturation [18,19] with testosterone (secreted by both testes and ovaries) stimulating the androgen-dependent regions.

Adrenarche is not a marker for pubertal onset per se, as its activation is independent of the hypothalamic–pituitary–gonadal axis.

Growth acceleration begins in girls at an average age of 9.5 years, and 11 years in boys, with a peak in girls at an average age of 11.5 years and 13 years in boys, and an end in girls by age 14.5 years and in boys by 16.5 years. This growth acceleration is critical to determine adult height and depends on the activation of the growth hormone-insulin like growth factor (GH-IGF) axis, associated with the increase in sexual steroid production [20]. Indeed, estradiol (secreted by ovaries, or converted from testosterone in peripheral tissues) is responsible for growth plate maturation.

The net effect of puberty on adolescence is enormous. Children gradually evolve to biological adults but still need the emotional and cognitive maturity to become successful sociological adults. Epilepsy may make this evolution more complex with its associated stigma, dependency, and self-esteem issues.

4. Sexual development

Sexuality evolves during adolescence and early adulthood. Sexual debut is typically in the mid-late teenage years in the USA, Canada, Netherlands, UK, and Australia [21]. By age 18 years, 10–40% remain virgins; however, by age 25–29 only 5% remain virgins. Clearly, sexual debut overlaps with the time of transition from pediatric to adult care. Although "one night stands" occur occasionally, most sexual intercourse takes place in the context of an intimate relationship that evolves over time from kissing to petting to vaginal intercourse. Peer relationships may be troubled in youth with epilepsy and therefore likely to interfere with normal sexual development.

Early sexual debut has been associated with less condom use, more sexual partners, more non-consensual sex, more sexually transmitted diseases, more teenage pregnancies as well as more frequent externalizing and internalized behaviors and low self-esteem, particularly in girls [21]. Late sexual debut has different associations - late puberty, less use of alcohol/drugs, differing religion/cultural attachments (especially for girls), high academic expectations, friends who delay sex, being overweight, self perception as physically unattractive, and no romantic relationships. Based on these associations, it is perhaps not surprising that sexual debut may be earlier in youth with epilepsy. A careful questionnaire investigation in Norway studied all youth between 13 and 19 years of age in one county [22]. The response rate was a stunning 85%. There were 247 respondents with epilepsy and 16,916 controls. Those with epilepsy were more likely to report having had sexual intercourse (44% vs. 35% $p = 0.009$), had a lower mean age at first intercourse (14 vs. 15 years, $p = 0.001$), were more likely to fail to use contraception at last intercourse (33% vs. 22%, $p = 0.03$), and appeared more likely to have "forced sex" (12% vs. 2%, $p = 0.001$). It is possible that comorbid factors, especially ADHD, may account for some of these differences, since ADHD is associated with epilepsy and sexual precocity. Other factors may include cognitive problems, low self-esteem, social isolation, and stigma [21]. Whatever the reasons for the difference, it behoves the clinician caring for adolescents near the age of transition to ask about sexual activity.

There is not much literature about sexual performance and satisfaction restricted to transition age. When sexuality and epilepsy are studied in a wider age range, a number of important themes emerge.

Men with epilepsy, compared to controls, appear to have decreased libido, more erectile dysfunction, and lower confidence in their sexual performance based on several sexual function questionnaires [23]. Loss of interest in sex has been reported with carbamazepine, clobazam, clonazepam, oxcarbazepine, phenytoin, phenobarbital, pregabalin, primidone, and topiramate. Erectile dysfunction is mentioned in literature pertaining to carbamazepine, clonazepam, gabapentin, oxcarbazepine, phenobarbital, pregabalin, primidone, and topiramate [24].

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There seems little doubt that both men and women with epilepsy may have decreased serum testosterone levels as the result of interactions with AEDs, including carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and primidone. Some, but not all, of these AEDs are "enzyme inducers". In one study, 60 male adults with focal epilepsy varying in age from 18 to 60 years were compared to 50 controls without epilepsy [23]. Serum hormone assays showed no difference between patients and controls for total testosterone, free testosterone, bioactive testosterone, and androstenedione. There was a significant reduction in SHBG (sex hormone binding globulin) and DHEAS (dehydroepiandrosterone). However, all of the hormone levels were in the range associated with normal sexual function. Sexual dysfunction was strongly predicted by measures of depression and anxiety, suggesting that mood and psychological function are far more important than serum sex hormones for sexual function in men with epilepsy.

Women with epilepsy also have significant sexual problems. When 195 women with epilepsy (mean age 29 years) were compared with 48 controls, there was no significant relation between free testosterone and scores on a questionnaire that assessed "enjoyment potential of intercourse" and "preferred frequency of intercourse". There was a significant correlation between "preferred frequency of intercourse" and the number of seizures in the past three months, suggesting that seizures themselves, either through fatigue or some other mechanism, affect sexual desire in women [25].

A recent Indian study addressed this issue further by comparing scores on the Female Sexual Function Index for 60 women aged 18–45 years with age-matched controls [26]. Women with epilepsy had highly significant increases in sexual problems expressed by questionnaire items that assessed low sexual desire, few orgasms, low vaginal lubrication, and pain during intercourse. Correlates included psychiatric symptoms and possibly high seizure numbers.

In both sexes there is a suggestion that right temporal lobe epilepsy is most strongly associated with hyposexuality, although methodological issues make this association somewhat uncertain. After temporal lobectomy, sexual interest and activity may increase even if there is less than complete seizure control [27].

4.1. Sexuality and intellectual disability

Sexuality and stable relationships are complicated for youth with intellectual disability (ID). McGuire [28] summarized this issue very well "The challenge is to find a middle ground between the expression of sexual rights and protection from harm." "In many settings, an ethically and legally precarious position may occur when an adult with an intellectual disability desires a sexual interaction, whereas their guardian opposes it. Guardians have a dual responsibility to empower and protect persons with intellectual disability". Ailey provided a poignant anecdote about a young man and woman with mild-moderate intellectual disability in two separate group homes who wished to be married [29]. The legal guardians were not in favor and their institutions had no facilities for co-habitation.

Even though there has been a major change in respect for the rights of people with ID, "those with ID continue to experience prohibitive attitudes and restrictive practices about sexual expression" [28]. It is not clear how successful sexuality educational programs are for those with ID and what constitutes adequate training to allow sexuality-related decisions.

Finally, we were not able to find any publications about gay and lesbian youth with epilepsy but it is possible that epilepsy makes these issues more complicated.

5. Psychological development

All adolescents face a set of biological, psychological, and social changes that progressively shape their own personalities. While these changes present special challenges for all young people with chronic illness, youth with epilepsy are particularly likely to have behavioral and emotional problems that pose great challenges to their families and physicians, especially around the time of transition [30,31].

In the normal development of autonomy and identity, Erikson suggested 3 stages to adolescence – early (ages 10–13 years) with concrete thinking, middle (ages 14–17) with more analytic and abstract introspective thinking, and late (ages 18–21) with at least the beginning of adult reasoning [32]. In the early stages adolescents explore identity through identification and experimentation with the same gender "cliques". At the same time, there are the beginnings of separation from the family with contesting of family values, conflicts with the family, and a need for greater privacy. In the middle stage, separation issues continue and friendships become more consistent; however, positive and negative risk taking behaviors increase. In the late stage, risk taking behavior may continue with peer relationships becoming even more important. There is a growing appreciation of family values and more willingness to compromise. Romantic relationships become more mature with stronger mutual trust.

It has been estimated that for about 75% of adolescents, there is gradual successful adaptation to adult life. For 60%, there is occasional distress but without functional impairment. Perhaps 15% "sail through" without significant distress. Those with a disturbed early childhood are more likely to have problems in adolescence and the addition of epilepsy to this process may have a multiplying effect. In youths with epilepsy, gaining autonomy may be impaired by restrictions for activities such as driving as well as a greater need for family interactions and supervision. Identity and dependence may be altered by a sense of lack of good health and "carefree adolescence" along with difficulties in managing parental anxiety and missing or stopping AEDs. It may be more difficult to establish stable relationships. The unpredictable nature of epilepsy may also interfere with intimacy, sexuality, and social activities [33,34].

There are differences between those who develop epilepsy in childhood with persistence into adolescence and those who start their seizures in adolescence. In the former there is a persistent hope that the epilepsy will vanish. In the latter there may be a sense of punishment particularly if the epilepsy begins during puberty.

Despite the emphasis on the young person, there is considerable literature that indicates that family/parental coping skills are the strongest predictors of adjustment to chronic disease in general and epilepsy in particular [35]. Parental psychopathology may be particularly problematic when parents express critical and hostile views towards their child with epilepsy [36].

Epilepsy associated with severe developmental disorders, autistic spectrum disorder (ASD), and or intellectual disability (ID), represents a particular challenge. Behavior issues are strongly associated with developmental disability, family psychopathology may be less relevant, and specific subtypes have been associated with genetic loading [37]. Several practical conclusions can be drawn from the experience of neurobehavioral units dedicated to severe behavioral problems (e.g. aggression, self-injury, disruption, agitation, and tantrums) in adolescents and young adults with severe neurodevelopmental disorders. In the largest series published so far, the most common causes found for acute behavioral crises were "organic" in 28% (epilepsy in 14% and painful medical conditions in an additional 14%), environmental problems in 25% (including lack of specific educational treatment in 16% and adjustment disorder in 9%), and non-autistic spectrum disorder psychiatric conditions in 48% (including disorders such as catatonia, major depressive episodes, bipolar disorder, and schizophrenia). In 17% no clear etiological diagnosis emerged. Notably, among the epilepsy causes, a large proportion of new diagnoses of epilepsy emerged during the multidisciplinary assessment [38].

There is relatively sparse literature about the efficacy and safety of psychotropic medications in these patients with complex epilepsy and a good deal of concern is appropriate especially when polytherapy

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may result in significant drug interactions [39]. While caution is appropriate, mood stabilizers may be useful.

As general conclusions for this section, we note that epilepsy can interfere with the achievement of independence, with important behavioral and emotional consequences. These concerns must be discussed with the youth and the family needs to be encouraged to develop a sensible and realistic approach. Adverse psychological adjustment can take many forms during adolescence from opposition to extreme submission without a specific psychological profile.

6. Bone health

A final basic issue is the effect of epilepsy in adolescence on long-term bone health. Childhood and adolescence are critical periods for bone development. From birth through the end of pubertal growth, there are significant changes in growth with an increase in length of approximately threefold, sharp changes in the relative proportions of limb, body, and head size, and accumulation of large amounts of calcium and phosphate within the skeleton [40]. By the end of adolescence and into the twenties, peak bone mass or the amount of bony tissue destined to be present at the end of skeletal maturation is obtained. Peak bone mass is an important determinant of osteoporotic fracture risk. Factors influencing peak bone mass include sex hormones, the IGF-I system, physical activity, calcium, protein intake, illnesses, and medications [40]. Children and adolescents with epilepsy are at increased risk for fracture, reduced bone mineral density (BMD), and abnormalities in bone and mineral metabolism. Understanding the effects of AEDs on bone health is important to allow optimal development of bone and reduce the reported increased risks for abnormalities in bone health.

Antiepileptic drugs were first associated with adverse effects on bone on the late 1960s. Early reports describe significant increased risk of hypocalcemia, radiologic evidence of rickets, decreased BMD, and osteomalacia, particularly in persons treated with AED polytherapy [41,42]. Epidemiologically, the most vulnerable groups at risk are institutionalized persons, children, postmenopausal women, and older men [43].

Table 3
Implications for transition.

Brain development – Impulsive pleasure seeking and risky behavior may be the result of an imbalance between frontal and limbic maturation and should be anticipated.
Endocrinological development – Puberty has a major effect on development, personality, and behavior.
Sexual development – Peer relationship problems may interfere with normal sexual development. Sexual debut is early in youth with epilepsy and long-term sexual experiences are often unsatisfactory.
Psychological development – Normal developmental stages in adolescence may be disrupted by epilepsy. While epilepsy may contribute to adjustment problems, some of these issues are related to normal developmental concerns. Family dysfunction has a strong effect on maturation of adolescents with epilepsy. Severe behavior problems with intellectual disability and/or autistic spectrum disorder are not typically related to family dysfunction and have multiple etiologies.
Bone health – The degree of risk for and mechanisms of bone disorders in childhood-onset epilepsy are unclear. For those at increased risk, serum vitamin D and DXA screening may be useful along with supplemental vitamin D.

Fractures are increased two- to sixfold in persons with epilepsy when compared to the general population [44–47]. The increased risk is secondary to a combination of seizures (particularly generalized convulsive seizures) and long-term effects of AEDs on bone. It is important to recognize that AEDs, especially in high doses, may cause poor coordination which can also increase facture susceptibility. One sibling pair study compared measures of static and dynamic balance between siblings treated with AEDs and siblings on no AEDs [48]. Users of AEDs performed significantly worse on the measures with longer duration of AED therapy resulting in worse scores.

AEDs can result in effects on bone quality. Osteomalacia and rickets were described in early reports. Biopsy studies in the 1980s, however, found normal osteoid seam width and consistently normal or increased mineralization rates [49,50]. Investigators concluded from these results

Table 2
Antiepileptic drugs and effects on bone: fracture, bone mineral density, bone quality, and biochemical abnormalities.

AED	Fracture	BMD	Bone quality	Biochemical abnormalities
Carbamazepine	Increased (OR 1.18, 1.10–1.26)[45] (OR 1.81, 1.46–2.23)[47]	Mixed results in adults Limited decrease in controlled pediatric studies	No data	↓Calcium; ↓Phosphate; ↓25(OH)D; ↑PTH; ↑BTMs
Oxcarbazepine	Increased (OR 1.14, 1.03–1.26)[45]	Mixed results in adults No decrease in single controlled pediatric study	No data	↓25 (OH)D; ↑PTH; ↑BTMs
Phenytoin	Increased (OR 1.91, 1.58–2.30)[2]	Reduced in adults No decrease in single controlled pediatric study	No data	↓Calcium; ↓Phosphate; ↓25(OH)D; ↑PTH; ↑BTMs
Phenobarbital	Increased (OR 1.60, 1.16–2.19)[2]	Reduced in adults and children	Osteomalacia and rickets in early studies	↓Calcium; ↓Phosphate; ↓25(OH)D; ↑PTH; ↑BTMs
Topiramate	No data	No decrease in single controlled pediatric study	No data	↓Calcium; ↓PTH;↓bicarbonate; ↑BTMs
Valproate	Increased (OR 1.15,1.05–1.26)[45] (OR 1.10, 0.70–1.72)[47]	Mixed results Limited decrease in controlled pediatric studies	No data	↑Calcium, ↓25(OH)D, ↑BTMs
Gabapentin	Increased (OR 1.49, 1.10–2.02)[47]	Reduced in older men	No data	No reported abnormalities
Lamotrigine	No data	No reduction No decrease in single controlled pediatric study	No data	No reported abnormalities
Levetiracetam	No data	Mixed results No decrease in single controlled pediatric study	Rat study with evidence of reduced bone strength and bone formation	No reported abnormalities
Ketogenic diet	No data	Reduced in children	No data	↓25(OH)D

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that AED use results in a disorder of increased remodeling (osteoporosis) rather than abnormal mineralization (osteomalacia). More subtle cortical and trabecular changes may, however, occur.

Bone mineral density measurements in patients with epilepsy treated with AEDs are generally 10–16% below controls [51]. Men and women are similarly affected. Among children, reduced BMD has been demonstrated at axial and appendicular sites but the findings are not as consistent as in older adults [51,52].

Although not consistent, biochemical abnormalities associated with AED treatment have been demonstrated [43]. These findings are most often seen in patients treated with enzyme-inducing AEDs and include relatively low calcium phosphate, and 25(OH)D concentrations as well as relatively increased parathyroid hormone, markers of bone resorption, and markers of bone formation.

Regarding specific AEDs, there are variable effects in pediatric studies (See Table 2) [43,45,47,51–54]. Carbamazepine, oxcarbazepine, phenytoin, phenobarbital, valproate, and gabapentin are associated with increased risk of fracture. Phenobarbital and the ketogenic diet in controlled pediatric studies result in decreased BMD. Limited BMD decrease in controlled pediatric studies was found with carbamazepine and valproate. Oxcarbazepine, phenytoin, topiramate, lamotrigine, and levetiracetam did not affect BMD in limited controlled adult studies. Variable biochemical abnormalities have been reported.

The principal mechanism reported to explain AED-related changes in bone relates to cytochrome P450 enzyme-induced increased vitamin D metabolism. This results in decreased active vitamin D metabolites, reduced gastrointestinal absorption of calcium, relative hypocalcemia, increased parathyroid hormone, and decreased BMD as a means of restoring serologic calcium concentrations [43]. Basic studies evaluating the effect of enzyme-inducing AEDs support this proposed mechanism [55,56]. Recent studies, however, do not consistently find decreased vitamin D metabolites in association with either decreased BMD or increased bone turnover as demonstrated by elevated markers of bone formation and resorption [54]. In addition, AEDs that are not strong enzyme inducers (such as valproate) may also result in abnormalities in bone. Other reported mechanisms include impaired absorption of calcium, vitamin K deficiency, directs effects of AEDs to stimulate osteoclastic bone resorption, effects of reproductive hormones, genetic influence, and a potential role of epilepsy itself [43].

No specific guidelines exist for screening for bone disease in persons with epilepsy. Routine screening of 25(OH)D is justifiable. Dual-energy x-ray absorptiometry screening should be considered for persons with prolonged treatment, particularly if the patient has another risk factor for low BMD. Limited treatment studies have predominantly addressed adults. One randomized study in children found improvement in BMD with low- and high-dose supplementation. In children, the primary emphasis should be on prevention and screening [57].

7. Conclusions

There are many brain and systemic changes at the time of transition that influence the ability of adolescents to master the skills required for independent management of their epilepsy in adult care. In addition, psychological and sexual development may be affected. Both pediatric and adult health care providers need to align their style of delivery of care to these realities. Table 3 summarizes a few of the broad concerns that arise from this review.

Conflict of interest

The authors have no conflicts of interest relevant to this manuscript and have not received any financial support related to this manuscript.

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