Treatment of epilepsy in young adults

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Objectives

- Teenage epilepsy
  - JAE & JME
  - Clinical symptoms
  - Diagnosis
  - Treatment

- Transition issues

Incidence:
- 11-19 y 20-60/100,000
- < 11 y 4/1000 children with persisting epilepsy

Prevalence:
- 1/3 of all epilepsy patients are < 18 y

Quality of life

Appleton RE.; Seizure 1995
Epilepsy syndromes

- JME
  - Juvenile absence
  - GTCS on awakening
  - Childhood absence
  - Rolandic epilepsy
- Lennox-Gastaut syndrome
- Simple febrile seizures
- Benign myoclonic epilepsy
- Infantile spasms
- EMEE/EIEE
- Neonatal seizures

Age (y) at Seizure Onset

- JME: (13-19)
- Juvenile absence: (10-15)
- GTCS on awakening: (6-22)
- Childhood absence: (3-7)
- Rolandic epilepsy: (4-13)
- Lennox-Gastaut syndrome: (1-8)
- Simple febrile seizures: (6mo-5)
- Benign myoclonic epilepsy: (1-2)
- Infantile spasms: (6mo-1)
- EMEE/EIEE: (0-6wk)
- Neonatal seizures: (0-1mo)
Idiopathic (“Genetic”) Generalized Epilepsies

- Childhood Absence Epilepsy
- Juvenile Absence Epilepsy
- Juvenile Myoclonic Epilepsy
- Generalized Tonic-Clonic Seizures Alone

Adolescents epilepsy

IGE affects approx. 15-20% of all patients with epilepsy

(Jallon and Latour, 2005)
Genetic versus idiopathic

- ‘Idiopathic’ = presumed hereditary predisposition

- Genetic ≠ inherited
  - Importance of *de novo* mutations in both mild and severe epilepsies

- Critical problem of stigma in some parts of the world
Seizure types

Focal onset  Generalized onset  Unknown onset

Motor
- tonic-clonic
- clonic
- tonic
- myoclonic
- myoclonic-tonic-clonic
- myoclonic-atonic
- atonic
- epileptic spasms
- Non-Motor (absence)
  - typical
  - atypical
  - myoclonic
  - eyelid myoclonia

GTCS
JME
JAE
Juvenile absence epilepsy

- Genetic generalized epilepsies
- CAE/JAE differs by seizure frequency
- Incidence:
  - 2–3% of patients with adult epilepsy,
  - 8–10% of IGE
- Age of onset 8-20 y (9-13) of age
- No sex dominance
- Needs life-long treatment

- Absence seizures
- Not very frequent seizures
- GTCS may occur prior to ABS
- GTCS during the course (80%)
- Myoclonic jerks can occur (10-20%)
Typical absence - EEG

- Usually regular and symmetrical 3 Hz (2-4 Hz) spike-and-slow-wave complexes and may have multiple spike-and-slow-wave complexes.
- Abnormalities are bilateral, synchronous.
- Background activity: usually normal (occasionally: focal EDs; bilateral, occipital slowing)
Svært beh. Absence epi.
ILAE classification of the epilepsies

JAE

Seizure types*
- Focal
- Generalized
- Unknown

Etiology
- Structural
- Genetic
- Infectious
- Metabolic
- Immune
- Unknown

Epilepsy types
- Focal
- Generalized
- Combined Generalized & Focal
- Unknown

Co-morbidities

Epilepsy Syndromes

Juvenil myoclonic epilepsy

- Genetic generalized epilepsies
- Prevalence of 5-11% among all patients with epilepsy
- Age of onset in the adolescence
- Female predominance
- Often need life-long therapy

**Myoclonia:** Sudden, brief (<100 ms) involuntary, single or multiple contraction(s) of muscles(s) or muscle groups of variable topography (axial, proximal limb, distal).

**JME:** Characterized by mandatory or typical myoclonic seizures alone or combined with generalized tonic–clonic seizures (GTCS) and/or absence seizures (ABS)

- **Myoclonic jerks (MJ)**
  - Fully conscious state
  - Predominate in the upper limbs
  - Usually on awakening.

- **GTCS may occur in 50–80%**
- **Absences in only 15–30% (?)**
JME - EEG

- Generalized spikes, polyspikes, spike-wave complexes, or combinations of these

- Provoking factors for JME discharges
  - Higher mental activities like speaking, reading, writing, arithmetic calculation, and spatial construction (Matsuoka et al., 2000)
  - Perioral reflex myoclonias induced by either reading or speaking (Mayer et al., 2006)
  - Photoconvulsive responses (30%)
ILAE classification of the epilepsies

- Seizure types:
  - Focal
  - Generalized
  - Unknown

- Epilepsy types:
  - Focal
  - Generalized
  - Combined Generalized & Focal
  - Unknown

- Etiology:
  - Structural
  - Genetic
  - Infectious
  - Metabolic
  - Immune
  - Unknown

JME Co-morbidities

Epilepsy Syndromes
Box 1
Juvenile myoclonic epilepsy (JME) diagnostic criteria and clinical phenotypes.

<table>
<thead>
<tr>
<th>Diagnostic criteria for JME (adapted from Kastelein-Nolst Trenité DG et al, Epilepsy Behav 2013)</th>
<th>Class I</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Myoclonic jerks without loss of consciousness repeatedly occurring on awakening, i.e., within 2 h after awakening</td>
<td>Class I</td>
</tr>
<tr>
<td>2. EEG (routine, sleep, or sleep deprivation) that shows normal background and ictal generalized high amplitude polyspikes (and waves) with concomitant myoclonic jerks</td>
<td></td>
</tr>
<tr>
<td>3. Normal intelligence</td>
<td></td>
</tr>
<tr>
<td>4. Age at onset of between 10 and 25 years</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Class II</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Myoclonic jerks predominantly occurring on awakening</td>
<td>Class II</td>
</tr>
<tr>
<td>2. Myoclonic jerks facilitated by sleep deprivation and stress and provoked by visual stimuli and praxis or GTCSs preceded by myoclonic jerks</td>
<td></td>
</tr>
<tr>
<td>3. EEG shows a normal background and at least once interictal generalized spike or poly-spike and waves with some asymmetry allowed with or without myoclonic jerks</td>
<td></td>
</tr>
<tr>
<td>4. No mental retardation or deterioration</td>
<td></td>
</tr>
<tr>
<td>5. Age at onset of between 6 and 25 years</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>JME clinical phenotypes (adapted from Martínez-Juárez IE et al, Brain 2005)</th>
<th>Classic JME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adolescence onset of myoclonic, tonic-clonic and clonic-tonic-clonic seizures with or without rare-to-infrequent absences and an EEG with 4–6 Hz polyspike-wave complexes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CAE evolving to JME</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Onset with absences with 3–4 Hz spike and wave complexes before aged 12 and then developed JME</td>
</tr>
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</table>

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<thead>
<tr>
<th></th>
<th>JME with adolescent absence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset with absences with 3–5 Hz spike and polyspike and wave complexes aged 12 or older mixed with JME</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>JME with astatic seizures</th>
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<tbody>
<tr>
<td></td>
<td>Astatic seizures mixed with JME</td>
</tr>
</tbody>
</table>
Prognosis of JME

- Benign epileptic syndrome
- Easy to control seizures
- Lifelong therapy is often needed

Large cohort study:
- N=6600 patients with epilepsy
- N= 240 JME
- Only 48% of patients were seizure free in the previous year
- Refractory cases (30-50%), 25% of them were seizure free in the previous year

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Refractory</th>
<th>Non-refractory</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sz free</td>
<td>30 (25%)</td>
<td>84 (71%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Only MJ or Abs</td>
<td>14 (11%)</td>
<td>16 (13%)</td>
<td></td>
</tr>
<tr>
<td>GTCS +/- MJ or Abs</td>
<td>69 (57%)</td>
<td>15 (13%)</td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up or death</td>
<td>8 (7%)</td>
<td>4 (3%)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 1
Clinical and demographic characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>240</td>
</tr>
<tr>
<td>M:F ratio</td>
<td>94:146</td>
</tr>
<tr>
<td>Current age (y)</td>
<td>38 (SD 11.7)</td>
</tr>
<tr>
<td>Age at sz onset (y)</td>
<td>14.2 (SD 4.5)</td>
</tr>
<tr>
<td>Age at diagnosis (y)</td>
<td>15.6 (SD 4.9)</td>
</tr>
</tbody>
</table>

#### Clinical phenotype
- **Classic**: 212 (88%)
- **CAE evolving into JME**: 14 (6%)
- **JME with adolescent Abs**: 9 (4%)
- **JME with astatic sz**: 5 (2%)

#### Past medical history
- **Febrile convulsions**: 10 (4%)
- **Delayed language development**: 5 (2%)
- **Prematurity**: 5 (2%)
- **Asperger's syndrome**: 3 (1%)
- **Type 1 DM**: 4 (2%)
- **Nonrelevant**: 175 (73%)

#### Family history of epilepsy
- **JME in first degree**: 3 (1%)
- **Non-JME in first degree**: 35 (15%)
- **JME in other members**: 3 (1%)
- **Non-JME in other members**: 26 (11%)

M – male; F – female; y – years; sz – seizures; CAE – childhood absence epilepsy; JME – juvenile myoclonic epilepsy; Abs – absences; DM – diabetes mellitus.
Fig. 1. Total AED used in the group with refractory seizures and the group with non-refractory seizures. Legend: Total number of each AED ever prescribed in the group with refractory seizures and the group with non-refractory seizures. ACZ — acetazolamide, CBZ — carbamazepine, CLB — clonazepam, CZP — clonazepam, DZP — diazepam, ESM — ethosuximide, GBP — gabapentin, LAC — lacosamide, LEV — levetiracetam, LTG — lamotrigine, MDZ — midazolam, OXC — oxcarbazepine, PB — phenobarbital, PER — perampanel, PGB — pregabalin, PHT — phenytoin, PIR — piracetam, PRM — primidone, STM — sulthimine, TPM — topiramate, VGB — vigabatrin, VPA — valproic acid, ZNS — zonisamide.
Remission and relapse of JAE and JME

- **Remission rates**
  - JME: 33 to 88%
  - JAE: 21–89%

- **Relapse rate**
  - JAE and JME similar
  - High (80-100%) for both groups who had been in remission, after AED withdrawal
  - Lack of long-term data
Fig. 3. Relapse% observed in those withdrawn and not withdrawn from AEDs, after at least 2 years seizure freedom.

Remission and relapse of JAE and JME

Remission rates
- JME: 33 to 88%
- JAE: 21–89%

Relapse rate for both JME and JAE patients who had been in remission, after AED withdrawal (long-term?)

Conclusion:
- Remission rates for JAE and JME was lower than expected.
- Relapse rates off AEDs were similar for JAE and JME, and at least twice as high as for those remaining on AEDs,
- Further remission was not invariable on restarting AEDs
The aim:

- to investigate the long-term seizure outcome in patients with JME after a follow-up of at least 25 years and
- to identify factors that are predictive for the seizure outcome.

**Poor prognosis**

- GTCS preceded by BMJ
- Long duration until seizure freedom is reached
- Polytherapy

**Favorable prognosis**

- Remission of GTCS under AED treatment is predictive of a long-term seizure-free outcome.
- The occurrence of PPRs significantly increase the chance of seizure recurrence after AED discontinuation.
- A shorter duration of epilepsy until seizure freedom is reached.
Management of epilepsy in teens

"Transition" and "transfer" from pediatric to adult care

- Dynamic, planned and structured process
- Between age 12-18
- Where to transfer patients?
  - GP/specialist/hospital service
  - Adult neurologist’s experience in dealing with "adult issues" (sex, contraception, pregnancy, driving, employment regulations, etc.)
  - Pædiatricians experience in treating childhood epilepsies
  - Children with learning disabilities
  - Patients interest - FOCUS
- Transition clinic – organisation/staff
Patient population in adolescent

- Epilepsy since childhood (50% persists)
- Newly diagnosed epilepsy in teens
- Recidive childhood epilepsy
Quality of life along life span

Seizure

Comorbidity

Psycho-social factors
TAKING OVER EPILEPSY FROM THE PAEDIATRIC NEUROLOGIST

Philip E M Smith, Sheila J Wallace

J Neurol Neurosurg Psychiatry 2003;74(Suppl 1):i37–i41

Box 1: Principles of consulting with teenagers with epilepsy

- See the teenager in a clinic setting with other teenagers or adults
- Focus the consultation on the teenager rather than the parents—for example, invite the teenager to introduce their parents or carer
- Discuss with the teenager adult topics such as alcohol, driving, pregnancy, and contraception
- Speak to the teenager alone during the consultation; an opportunity arises if the physical examination is conducted in another room
- Give the opportunity to speak to an epilepsy specialist nurse; like many adults, teenagers often open up to a nurse more than to a doctor
- Offer written material on relevant aspects of epilepsy. Sending copy letters to patients empowers them and acts as continuing education and encouragement
- Encourage carers to allow the teenager an appropriate amount of responsibility—for example, for his or her own tablets

Transition clinic – staff

Pediatrician
Neurologist
Epilepsy nurses
Psychologist
Psychiatrist
Social worker
Diagnosis & classification

History
- Seizure description (semiology)/video film
- Clinical symptoms/neurological signs (cognitive function)
- EEG
- MRI (SPECT, PET)
- Laboratory tests (genetic)

Klassifikation:

Clinical data
- Neuroimaging
- Lab tests

Seizure type → Epilepsy type (Syndrome) → Etiology (diagnosis)

Therapy
The Art of Antiepileptic Treatment

Matching the Drug to the Patient
No principal differences in treatment strategies
  - Seizure freedom
  - Monotherapy
  - Side-effect profile (weight, psychic, cosmetic)
  - Interactions (p-pills)

Targeted treatment (JME/JAE)
  - Identify medical intractability

Involving the teens in decision making
  - Information, education, lifestyle
Case 2 /UB

- Normal birth, development, fam. disp.: non

- Epilepsy since 13 y of age – dg 2 years later, JAE
  - Sz types: absences, no GTCS
  - EEG: gen. paroxysms of SPW complexes 3,5-4 Hz
  - MRI norm.

- Th: LTG+VPA
  - No side-effects
  - SZ free (??)

- Comorbid depression (fam.)
UB cont.

- Transition in 2014 (19 y)
  - SZ-free??
  - Compliance
  - Cognitive problems

- 2016-17
  - Tendence to absences- precipitated often
  - Never been SZ free
  - Th: LTG 200 mg + VPA 1500 mg
  - Needs immediate help
  - vEEG
  - Therapy changed: VPA → LEV → ESM (+LTG)
  - NEW: GTCS ??
Inflencing factors on choosing AED

<table>
<thead>
<tr>
<th>AED-specific factors</th>
<th>Patient-specific factors</th>
<th>Country-specific factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sizure type or epilepsy syndromes</td>
<td>Genetic background</td>
<td>AED availability</td>
</tr>
<tr>
<td>Dose-dependent AE</td>
<td>Age</td>
<td>AED prices</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Gender</td>
<td>Insurrance</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td>Comedication</td>
<td></td>
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<tr>
<td>Carcinogenicicty</td>
<td>Comorbiditet</td>
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<tr>
<td>Pharmacokinetic</td>
<td>Insurrance</td>
<td></td>
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<tr>
<td>Interactions</td>
<td></td>
<td></td>
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<tr>
<td>Administration forms</td>
<td></td>
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</tr>
</tbody>
</table>
AEDs availability

- Phenobarbital (1912)
- Phenytoin (1938)
- Primidone (1952)
- Ethosuximide (1955)
- Carbamazepine (1965)
- Valproate (1979)
- Gabapentin (1996)
- Lamotrigine (1993)
- Tiagabine (1996)
- Topiramate (1997)
- Pregabalin (2001)
- Levetiracetam (2006)
- Zonisamide (2008)
- Carbamazepin (2009)
- Ethosuximid (2010)
- Valproat (2010)
- Oxcarbazepin (2010)
- Lacosamide (2009)
- Vigabatrin (2009)
- Rufinamide (2009)
- Brivaracetam (2016)

- Brivaracetam > 4 y
- Lacosamide > 4 y
- Perampanel > 12 y
- Eslicarbazepine > 6 y
- Rufinamide > 4 y
Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes

*Tracy Glauser, †Elinor Ben-Menachem, ‡Blaise Bourgeois, §Avital Cnaan, ¶Carlos Guerreiro, #Reetta Kälviäinen, **Richard Mattson, ††Jacqueline A. French, ‡‡Emilio Perucca, §§Torbjorn Tomson for the ILAE subcommission of AED Guidelines

*Comprehensive Epilepsy Center, Division of Neurology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio, U.S.A.; †Institution for Clinical Neuroscience, Sahlgrenska Academy, University of Göteborg, Göteborg, Sweden; ‡Department of Neurology, The Children's Hospital and Harvard Medical School, Boston, Massachusetts, U.S.A.; §Division of Biostatistics and Study Methodology, Center for Translational Science, Children's National Medical Center, Washington, District of Columbia, U.S.A.; ¶Department of Neurology, University of Campinas (UNICAMP), Hospital das Clínicas, Campinas, Sao Paulo, Brazil; #Department of Neurology, Kuopio Epilepsy Center, Kuopio University Hospital, Kuopio, Finland; **Department of Neurology, Yale University School of Medicine, Yale New Haven Hospital, New Haven, Connecticut, U.S.A.; ††Comprehensive Epilepsy Center, New York University Langone Medical Center, New York, New York, U.S.A.; ‡‡Clinical Pharmacology Unit, Institute of Neurology, IRCCS C. Mondino Foundation, University of Pavia, Pavia, Italy; and §§Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden
## Summary of Evidence and Recommendations

*Generalized onset seizures*

<table>
<thead>
<tr>
<th>Seizure type or epilepsy syndrome</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Level of efficacy and effectiveness evidence (in alphabetical order)</th>
</tr>
</thead>
</table>
| GTC: Adults                      | 0       | 0        | 23 4      | Level A: None  
Level B: None  
Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA  
Level D: GBP, LEV, VGB |
| GTC: Children                    | 0       | 0        | 14        | Level A: None  
Level B: None  
Level C: CBZ, PB, PHT, TPM, VPA  
Level D: OXC |
| Absence seizures                 | 0 1     | 0        | 6 1       | Level A: (None), *ESM, VPA  
Level B: None  
Level C: (ESM), LTG, (VPA)  
Level D: None  
*may aggravate GTCS |
# Summary of Evidence and Recommendations

## Epilepsy syndromes

<table>
<thead>
<tr>
<th>Seizure type or epilepsy syndrome</th>
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<th>Class II</th>
<th>Class III</th>
<th>Level of efficacy and effectiveness evidence (in alphabetical order)</th>
</tr>
</thead>
</table>
| BECTS                            | 0       | 0        | 2         | Level A: None  
Level B: None  
Level C: CBZ, VPA  
Level D: GBP, LEV, OXC, STM |
| JME                              | 0       | 0        | 0         | Level A: None  
Level B: None  
Level C: None  
Level D: CZP, LTG*, LEV, TPM, VPA, ZNS  
Level E: Others  
Level F: CBZ*, GBP, OXC*, PHT*, TGB, VGB |

*may aggravate myoclonic seizure types, should be used with caution
Diagnosis and management of epilepsies incl. recommendations for the pharmacological treatment of JME.

- **Absolut 1st line:** Valproic acid
- **1st line:** lamotrigine, levetiracetam and topiramate
- **2nd line:** lamotrigine, levetiracetam, sodium valproate or topiramate as adjunctive therapy
- **3rd line:** clobazam, clonazepam or zonisamide

**Valproate in the treatment of epilepsy in women and girls**

Pre-Publication: Summary of Recommendations from a joint Task Force of ILAE-Commission on European Affairs* and European Academy of Neurology (EAN)** - 2015 (www.ilae.org)

The UK National Institute for Health and Care Excellence (NICE) guidelines (2017)
AEDs negative effect

<table>
<thead>
<tr>
<th>Absences</th>
<th>Myoclonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Carbamazepine</td>
<td>• Carbamazepine,</td>
</tr>
<tr>
<td>• Oxcarbazepine</td>
<td>• Oxcarbazepine,</td>
</tr>
<tr>
<td>• Eslicarbazepine (?)</td>
<td>• Eslicarbazepine (?)</td>
</tr>
<tr>
<td>• Phenytoin</td>
<td>• Lamotrigine</td>
</tr>
<tr>
<td>• Gabapentin</td>
<td>• Gabapentin</td>
</tr>
<tr>
<td>• Pregabalin</td>
<td>• Pregabalin</td>
</tr>
<tr>
<td>• Tiagabin</td>
<td>• Tiagabin</td>
</tr>
<tr>
<td>• Vigabatrin</td>
<td>• Vigabatrin</td>
</tr>
<tr>
<td>• Primidon(?)</td>
<td></td>
</tr>
</tbody>
</table>
Case 1 / DS

- Debut i 11 y (2004)
- JAE: Absencer og seldom GTCS
- EEG (2010): 4-5 Hz generalized paroxysms with PSW, precipitated by HV (IGE)
- Therapy:
  - 2004 Lamotrigine – not sufficient
  - 2008 Ethosuximid additive (+clobazam) – still not SZ-free
- Clinical symptoms:
  - Still not Szfree
  - myoclonic jerks??
  - sleep problems
- Polysomnography: norm.
- Therapy:
  - Lamotrigine for epilepsy
  - Melatonin for sleepdisturbance
  - Sifrol (obs. restless-leggs)
REVISION of diagnosis and treatment

- 2012 – referred to Glostrup
  - Suspect for side-effects for LTG
  - vEEG SWP, myoclonia with norm. ictal EEG, no clinical SZ but interictal PSW.
  - New PSG – norm

- Shift from LTG to LEV + ETX  →  SZ free,
- Withdrawal of Sifrol  →  no myoclonia anymore

Improved of quality of life in the last 5 years!
Concluding remarks

- Transition
- Social issues
  - Family
  - Driving
  - Education
- Quality of life
- Comorbidity
- Diagnostic challenges
- Targeted treatment
- Compliance
- Withdrawal