Tuesday, 1:00 – 2:30, B1

Use of Antipsychotics & Anticonvulsants in IDDs

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Objective:

Identify and prevent the potential adverse interactions between antipsychotics and anticonvulsants used in the treatment of individuals with IDDs.

Notes:

The Use of Antipsychotics & Anticonvulsants in IDDs
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Professional Information

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Disclosure

- There are no financial affiliations or compensations related to the content of this presentation.

Medications Discussed

- **Antipsychotics:**
- aripiprazole (Abilify®, Aristada®)
- asenapine (Saphris®)
- brexpiprazole (Rexulti®)
- cariprazine (Vraylar®)
- clozapine (Clozaril®, FazaClo®, Versacloz®)
- iloperidone (Fanapt®)
- lurasidone (Latuda®)
- olanzapine (Zyprexa®)
- paliperidone (Invega®)
- quetiapine (Seroquel®)
- risperidone (Risperdal®)
- ziprasidone (Geodon®)

Medications Discussed

- **Anticonvulsants:**
- acetazolamide (Diamox®)
- brivaracetam (Briviact®)
- carbamazepine (Tegretol®, Carbatrol®, Equetro®)
- clobazam (Onfi®)
- divalproex sodium (Depakote®)
- eslicarbazine (Aptiom®)
- ethosuximide (Zarontin®)
- ezogabine (Potiga®)
- fosphenytoin (Cerebyx®)
- felbamate (Felbatol®)
- gabapentin (Neurontin®)
- lacosamide (Vimpat®)

Medications Discussed

- **Anticonvulsants** (cont.):
- lamotrigine (Lamictal®)
- levetiracetam (Keppra®)
- methsuximide (Celontin®)
- oxcarbazepine (Trileptal®)
- perampanel (Fycompa®)
- pregabalin (Lyrica®)
- phenytoin (Dilantin®, Phenytek®)
- rufinamide (Banzel®)
- tiagabine (Gabitril®)
- topiramate (Topamax®, Qudexy XR®, Trokendi XR®)
- vigabatrin (Sabril®)
- zonisamide (Zonegran®)

Presentation Overview

1. Epidemiology of psychopathology in IDDs
2. Epidemiology of epilepsy in IDDs
3. Epidemiology of psychopathology in epilepsy
4. The intersection of IDDs, MI and epilepsy
5. Pharmacotherapy of psychopathology in IDDs
6. Pharmacotherapy of epilepsy in IDDs
7. Pharmacotherapy of psychopathology in epilepsy

Presentation Overview

8. Pharmacotherapy of combined IDD, MI and epilepsy
9. Potential adverse events, drug-drug interactions, and proconvulsant effects in the treatment of comorbid disorders

Epidemiology of Psychopathology in IDDs

Epidemiology of Psychopathology; General

- One study examined rates of behavior problems and psychopathology among children with DDs compared to both chronologic age (CA) and mental age (MA) matched comparison groups.
- Significant group differences were found for ADHD, most notably the inattentive subtype, which was over three times as prevalent in the DD group. In the MA-match analyses, the DD group demonstrated significantly higher rates of the hyperactive subtype.
- The prevalence of Social Phobia was significantly higher in the DD than the typical development sample for the MA-match analyses.

Caplan, et al., 2015

DISC modules	DD sample[a]	CA-match analyses				MA-match analyses			
		TD sample[a] (age 9)	X^2	Relative risk (DD:TD)	OR	TD sample[a] (age 6)	X^2	Relative risk (DD:TD)	OR
Any mental disorder	57.1	37.1	2.81†	1.54:1	2.26	34.3	3.68†	1.66:1	2.56
ADHD[b] (any subtype)	42.9	20.0	4.24*	2.14:1	3.00	14.3	7.00**	3.00:1	4.50
ADHD[b]-inattentive subtype	40.0	17.1	4.48*	2.34:1	3.22	11.4	7.48**	3.50:1	5.17
ADHD[b]–hyperactive subtype	25.7	14.3	1.43	1.80:1	2.08	5.7	5.29*	4.50:1	5.71
Oppositional defiant disorder	31.4	20.0	1.20	1.57:1	1.83	20.0	1.20	1.57:1	1.83
Separation anxiety disorder	11.4	0	4.24*	–	–	8.6	0.16	1.32:1	1.38
Social phobia	17.1	8.6	1.15	1.99:1	2.21	0	6.56*	–	–

† $p < .10$.
* $p < .05$.
** $p < .01$.
[a] $n = 35$.
[b] ADHD = Attention Deficit Hyperactivity Disorder.

Caplan, et al., 2015

Epidemiology of Psychopathology: General

- A UK study found that more than a third- 40.9% (clinical diagnoses) or 35.2% (DC–LD diagnoses)- of an adult, ID cohort had mental ill-health.
- Those point prevalence rates were higher than those observed in the UK general population.

Cooper, et al., 2007c

Point prevalence rates of mental ill-health as defined by clinical, DC–LD, ICD–10–DCR, and DSM–IV–TR diagnostic criteria

Diagnostic category	Clinical diagnosis (n=1023) %	DC–LD diagnosis (n=1023) %	ICD–10–DCR diagnosis (n=1023) %	DSM–IV–TR diagnosis (n=1023) %
Psychotic disorder[1]	4.4	3.8	2.6	3.4
Affective disorder	6.6	5.7	4.8	3.6
Anxiety disorder[2]	3.8	3.1	2.8	2.4
OCD	0.7	0.5	0.2	0.2
Organic disorder	2.2	2.1	1.9	1.7
Alcohol/substance use disorder	1.0	0.8	0.8	0.8
Pica	2.0	2.0	0	0.9
Sleep disorder	0.6	0.4	0.2	0.2
ADHD	1.5	1.2	0.5	0.4
Autistic-spectrum disorder	7.5	4.4	2.2	2.0
Problem behaviour	22.5	18.7	0.1	0.1
Personality disorder	1.0	0.8	0.7	0.7
Other mental ill-health	1.4	0.8	0.7	0.4
Mental ill-health of any type, excluding problem behaviours and autistic-spectrum disorder[2]	22.4	19.1	14.5	13.9
Mental ill-health of any type, excluding autistic-spectrum disorder[2]	37.0	32.8	14.6	14.0
Mental ill-health of any type, excluding problem behaviours[2]	28.3	22.4	16.5	15.6
Mental ill-health of any type[2]	40.9	35.2	16.6	15.7

ADHD, attention-deficit hyperactivity disorder; OCD, obsessive–compulsive disorder.
1. Includes schizoaffective disorders.
2. Excludes specific phobias.

Cooper, et al., 2007c

Epidemiology of Psychopathology: Self-injurious Behavior

- A UK study found the point prevalence of self-injurious behavior (SIB) to be 4.9%, the 2-year incidence 0.6%, and the 2-year remission rate 38.2%.
- At any point in time, the point prevalence of SIB was accounted for by both new onset, and by enduring SIB, with enduring SIB predominating.

Cooper, et al., 2009a

Epidemiology of Psychopathology: Aggressive Behavior

- The same UK group found the point prevalence of aggressive behavior was 9.8%, 2-year incidence was 1.8%, and, for the adults who had aggressive behavior, the 2-year remission rate was 27.7%.
- Prevalence was accounted for by both new onset aggressive behavior and enduring aggressive behaviors.

Cooper, et al., 2009b

Epidemiology of Psychopathology: Psychosis

- Cooper's group found the point prevalence of psychosis to be 2.6%-4.4% depending upon the diagnostic criteria used; 2-year incidence of psychotic episode was 1.4%, 2-year incidence of first episode of psychosis was 0.5%, and, of people in episode at entry, the remission rate in the 2-year period was low, at 14.3%.

Cooper, et al., 2007a

Epidemiology of Psychopathology: Mood Disorders

- Cooper's group also found that the point prevalence of affective (mood) disorders was higher in the ID population (than that reported previously for the general population): 3.8% for depression and 0.6% for mania.
- In addition, 1.0% had bipolar disorder, currently in remission, and 0.1% first episode of mania, currently in remission.

Cooper, et al., 2007b

Epidemiology of Epilepsy in IDDs

Epidemiology of Epilepsy in IDDs

- A review article reported that in general samples of people with IDs, the pooled estimate (from 38 studies) of epilepsy prevalence was 22.2%.
- For samples of people with Down syndrome, excluding two studies focusing on older people, the prevalence rate was lower, with the pooled estimate (from 11 studies) being 10.3%.

Robertson, et al., 2015

Epidemiology of Epilepsy in IDDs

- A systematic review of outcomes in ASDs found that the overall percentage of participants with epilepsy at follow-up ranged between 1.8% in those under 12 years of age (the majority of whom did *not* have an ID) and 23.7% of those over 12 years of age, of whom the majority *did have* an ID.
- These are significantly greater percentages than those reported in the literature for the general population, but are similar to those found for IDs.

Woolfenden, et al., 2012

Epidemiology of Epilepsy in IDDs

- The causes of IDDs and epilepsy are increasingly recognized to be genetic, based on: chromosomal microarray analysis to identify copy number variants; gene panels; and, whole-exome sequencing.
- A specific genetic diagnosis may guide care by pointing to comorbid disorders and best therapy.

Devinsky, et al., 2015

Examples of recurrent copy number variants associated with ID, epilepsy, and other neurodevelopmental phenotypes

Copy number variant	Deletion or duplication	Associated phenotypes
1p36	Deletion/duplication	ID, ASD (Del), EPI (Del)
1q21.1	Deletion/duplication	ID, ASD, SCHZ, EPI
2p16.3	Deletion	ID, SCHZ, EPI
2q13	Deletion/duplication	ID, ASD, EPI (Del)
2q37	Deletion	ID, ASD, EPI
3q29	Deletion/duplication	ID (Del), SCHZ, EPI (Del)
4p16.3 (Wolf-Hirschhorn syndrome)	Deletion	ID, EPI
4q21.21-q21.22	Deletion	ID, ASD, EPI
5q35.2-q35.3 (Sotos syndrome)	Deletion	ID, EPI
7q11.22-q11.23	Deletion/duplication	ID, EPI, ASD (Dup)
9q34.3 (9q subtelomeric syndrome)	Deletion	ID, ASD, EPI
15q11.2	Deletion	ID, ASD, SCHZ, EPI
15q11-q13 (Prader-Willi/Angelman syndrome)	Duplication/deletion	ID, ASD (Dup), SCHZ (Dup), EPI

Examples of recurrent copy number variants associated with ID, epilepsy, and other neurodevelopmental phenotypes

Copy number variant	Deletion or duplication	Associated phenotypes
15q13.3	Deletion/duplication	ID, ASD, SCHZ (Del), EPI
16p11.2	Deletion/duplication	ID, ASD, SCHZ (Dup), EPI
16p12.1	Deletion	ID, ASD, EPI
16p13.11	Deletion/duplication	ID, SCHZ (Dup), EPI (Del)
17p12-p11.2 (Potocki-Lupski/Smith Magenis syndromes)	Deletion/duplication	ID, ASD (Dup), EPI
17p13.3-13.2 (Miller-Dieker syndrome)	Deletion	ID, ASD, EPI
17q12	Deletion/duplication	ID, ASD, SCHZ (Del), EPI
17q21.3	Deletion	ID, ASD, EPI
22q11 (Velocardiofacial/DiGeorge syndrome)	Deletion/duplication	ID, ASD (Dup), SCHZ (Del), EPI
22q11.2	Deletion	ID, ASD, EPI
22q13 (Phelan-McDermid syndrome)	Deletion	ID, ASD, EPI
Xp22.1	Deletion	ID, ASD, EPI

Epidemiology of Epilepsy in IDDs

- The prevalence of epilepsy increases with the severity of the IDD. Among 692 patients with childhood-onset epilepsy followed for 20-30 years, 147 (21%) had IDD with epilepsy. Of those 147 cases, 53% had severe/profound IDD compared to 24% with moderate IDD and 24% with mild IDD.

Devinsky, et al., 2015

Epidemiology of Epilepsy in IDDs

- Seizure *type* is also influenced by the severity of the IDD. Focal epilepsies predominate in those with mild IDD (69%; 17% with symptomatic generalized epilepsy), similar to those with normal intelligence, while symptomatic generalized epilepsies predominate in those with severe IDD (67%; 29% with focal epilepsy).
- Seizure type is related to rates of remission, with some types being more treatment-resistant.

Devinsky, et al., 2015

Role of IDD in epilepsy types and remission

	Remission, %	Intractable epilepsy, %
All epilepsies		
Mild IDD	49	14
Moderate IDD	32	38
Severe/profound IDD	24	55
Focal epilepsy only		
Normal intelligence	68	15
Mild IDD	57	10
Moderate IDD	28	30
Severe/profound IDD	28	44

Devinsky, et al., 2015

Epidemiology of Psychopathology in Epilepsy

Epidemiology of Psychopathology in Epilepsy

- In the task force report from the International League Against Epilepsy (ILAE), the authors note that epidemiological studies in a number of different countries, and over a long period of time, have yielded reasonably consistent results with regard to the rates of psychiatric disorder in children with epilepsy, which have ranged from around 35% to 50%.

Sillanpää, et al., 2016

Epidemiology of Psychopathology in Epilepsy

- ADHD is under-diagnosed and under-treated in children with epilepsy. Approximately 30% of children with epilepsy have ADHD.
- There is a broad differential diagnosis for the causes of ADHD symptoms in children with epilepsy, including the epilepsy itself and some antiepileptic drugs.

Besag, et al., 2016b

Epidemiology of Psychopathology in Epilepsy

- Anxiety and depression are common in children and adolescents with epilepsy, affecting one-quarter to one-third of patients.
- Multiple epilepsy-related, psychological and genetic-familial factors have been implicated in causing anxiety and depression in patients with epilepsy.

Dunn, et al., 2016

Epidemiology of Psychopathology in Epilepsy

- The overall research evidence suggests that schizophrenia-like psychosis is believed to be 6 to 12 times more likely to occur in people with epilepsy than in the general population.

Mendez, et al., 1993

The Intersection of IDDs, MI, and Epilepsy

The Intersection of IDDs, MI, and Epilepsy

- The previously cited ILAE task force report also noted that the prevalence of psychiatric disorder in children with complicated epilepsy, usually implying accompanying intellectual disability, is much higher, well over 50%.

Sillanpää, et al., 2016

The Intersection of IDDs, MI, and Epilepsy

- In another study, investigators looked at: (a) associations between epilepsy (or epilepsy-related factors) and neuropsychiatric comorbidities in patients with ID and (b) between ID and neuropsychiatric comorbidities in patients with epilepsy.

van Ool, et al., 2016

The Intersection of IDDs, MI, and Epilepsy

- There was an indication that having epilepsy was significantly related to higher rates of negative mood symptoms in adults and elderly with ID, including depressive symptoms, negative mood, and mood swings. Having epilepsy was, however, not associated with emotional disturbances. Most studies also did not demonstrate a significant association between the presence of epilepsy and behavioral problems

van Ool, et al., 2016

The Intersection of IDDs, MI, and Epilepsy

- Generally, the results indicated that more severe epilepsies (including generalized seizures), greater seizure severity, higher seizure frequency, and higher number of seizure types, were risk factors for behavioral problems and psychiatric disorders.

van Ool, et al., 2016

The Intersection of IDDs, MI, and Epilepsy

- Having ID was related to higher rates of ASD, postictal psychosis, and both psychotic and nonpsychotic disorders.
- The degree of the ID seemed relevant with respect to behavioral problems, a more severe ID being significantly associated with more behavioral problems in adults with epilepsy.

van Ool, et al., 2016

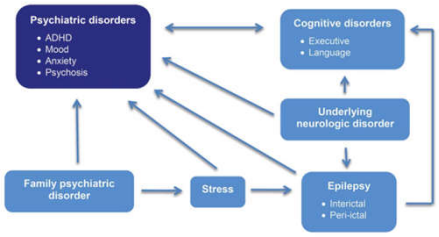
Summary of findings on neuropsychiatric outcomes in patients with ID and epilepsy

Presence of epilepsy	
Psychiatric characteristics	Behavioral problems
+ Negative mood [20]	+ Poor speech, being uncooperative, and disturbing others at night [21]
+ Depressive symptoms and unspecified disorders [19]	+ Severe sleep problems, which were related to irritability [25]
+ Lack of empathy, mood swings [23]	No association with behavioral disturbances [21], behavioral problems and social impairment [22], social skills [24], and physical aggression [26]
− Psychosis [18]	
No association with emotional disturbances [21] and psychopathology [22]	
Epilepsy-related factors	
Seizure type	Other
+ Generalized epilepsy: hyperactivity, noncompliance [27]	+ Higher age at onset: ASD [29]
+ More than 2 seizure types: ASD [29]	+ Febrile convulsions, females: irritability, agitation, and crying [27]
+ Seizure severity: possible psychiatric disorder [28]	− Loss of consciousness: psychiatric disorders
Seizure frequency	+ Sensory disabilities: behavioral problems [28]
+ Higher seizure frequency: possible psychiatric disorder [28]	+ AED adverse events: behavioral problems [28]
No association between active epilepsy and behavioral and emotional disturbances [21]	
ID	
Presence of ID	Level of ID
+ Nonpsychotic and psychotic disorders [32]	+ Moderate ID (vs. mild ID): hyperactivity, noncompliance, and inappropriate speech [28]
+ Autism spectrum disorder [31]	+ More severe ID: lethargy, stereotypic behavior [29]
+ Postictal psychosis [33]	

(+) = statistically significant positive association, (−) = statistically significant negative association. AED = antiepileptic drugs, ASD = autism spectrum disorder, ID = intellectual disability.

van Ool, et al., 2016

Factors contributing to the genesis and persistence of psychiatric disorders in patients with IDDs and epilepsy



Devinsky, et al., 2015

Pharmacotherapy of Psychopathology in IDDs

Pharmacotherapy of SIB

- In the UK, an expert panel's (all 258 consultant members on the mailing list of the Royal College of Psychiatrists' Learning Disability Faculty) first choices of medications for *SIB* were:
  - Antipsychotics- 49.1%
  - Antidepressants- 25.9%
  - Anti-anxiety drugs- 11.1%

Unwin & Deb, 2008

Pharmacotherapy of SIB

- The expert panel's first choices of *atypical antipsychotics* for SIB were:
  - Risperidone- 74.1%
  - Olanzapine- 12.0%
  - Quetiapine- 0.9%

Unwin & Deb, 2008

Pharmacotherapy of SIB

- The expert panel's first choices of *antidepressants* for SIB were:
  - Citalopram- 32.4%
  - Fluoxetine- 22.2%
  - Sertraline- 11.1%
  - Escitalopram- 9.3%

Unwin & Deb, 2008

Pharmacotherapy of Aggression

- In the UK, an expert panel's (all 258 consultant members on the mailing list of the Royal College of Psychiatrists' Learning Disability Faculty) first choices of medications for *aggression* were:
  - Antipsychotics- 80.6%
  - Anti-anxiety drugs- 12.0%
  - Antidepressants- 6.5%

Unwin & Deb, 2008

Pharmacotherapy of Aggression

- The expert panel's first choices of *atypical antipsychotics* for aggression were:
  - Risperidone- 78.7%
  - Olanzapine- 13.0%
  - Quetiapine- 1.9%

Unwin & Deb, 2008

Pharmacotherapy of Aggression

- The expert panel's first choices of *antidepressants* for aggression were:
  - Citalopram- 35.2%
  - Fluoxetine- 19.4%
  - Sertraline- 13.0%
  - Escitalopram- 10.2%

Unwin & Deb, 2008

Pharmacotherapy of Psychosis

- Any antipsychotic medication can be used to treat psychotic symptoms in individuals with IDDs, with the atypical agents being preferred over older agents.
- The choice of agent will be determined by the trade-off between efficacy and tolerance (side effect profile).

Pharmacotherapy of Mood Disorders

- The selective serotonin reuptake inhibitors (SSRIs) are the preferred medications for the treatment of depression in individuals with IDDs.
- The atypical antipsychotics are first line treatments for bipolar disorder/mania, unless there is comorbid epilepsy, in which case anticonvulsants with good mood stabilizing properties should be used first.

FDA-APPROVED INDICATIONS FOR ATYPICAL ANTIPSYCHOTICS IN C&A						
Disorders (ages)	**Antipsychotic agents**					
	ARI	**ASP**	**OLZ**	**PAL**	**QUE**	**RIS**
Schizophrenia (12-17)				X		
Schizophrenia (13-17)	X		X		X	X
BD-I, mania (10-17)		X			X	X
BD-I, mania or mixed (10-17)	X					
BD-I, mania or mixed (13-17)			X			
BD-I, depression (10-17)			X*			
Autistic disorder-associated irritability (5-17)						X
Autistic disorder-associated irritability (6-17)	X					

ARI= aripiprazole; ASP= asenapine; OLZ= olanzapine; PAL= paliperidone; QUE= quetiapine; RIS= risperidone.

* In combination with fluoxetine

Pharmacotherapy of Epilepsy in IDDs

Pharmacotherapy of Epilepsy in IDDs

- Therapy to control seizures should be individualized, with drug selection based on seizure types, epilepsy syndrome, concomitant medications, and comorbid disorders.
- There are limited comparative antiepileptic drug data in the IDD with epilepsy population.

Devinsky, et al., 2015

Pharmacotherapy of Epilepsy in IDs

- A Cochrane Review on pharmacological interventions for epilepsy in people with IDs determined that, in general, AEDs that are proven to be effective in the general epilepsy population are also effective for refractory epilepsy in people with ID.
- It was not possible for the authors to comment on the relative efficacy of medications, making clinical decisions difficult.

Jackson, et al., 2015

Pharmacotherapy of Epilepsy in IDs

- The treatment of refractory epilepsy does seem to differ if IDs are present.
- A Canadian study found that patients with ID were currently taking, and had been previously exposed to, a greater number of different AEDs. Patients with ID were also more likely to be taking at least one older AED and were more commonly treated with benzodiazepines.

Fridhandler, et al., 2012

Pharmacotherapy of Epilepsy in IDs

- A more recent study assessed the efficacy of newer AEDs in individuals with Angelman syndrome (AS) (~80-90% with AS have epilepsy).
- Newer AEDs, such as levetiracetam, lamotrigine, and clobazam, and, to a lesser extent, topiramate, appeared to be as effective- if not more so- as valproic acid and clonazepam, while offering more favorable side effect profiles.

Shaaya, et al., 2016

Pharmacotherapy of Epilepsy in IDs

- Another genetic syndrome with high prevalence of epilepsy (up to 90%) is tuberous sclerosis complex (TSC).
- A Dutch study of children with TSC and epilepsy found that vigabatrin was used by 94% of children, and was the first treatment in 48%.
- Vigabatrin was more effective than other AEDs (including VPA) when prescribed as first treatment.

Overwater, et al., 2015

Pharmacotherapy of Psychopathology in Epilepsy

Pharmacotherapy of Psychopathology in Epilepsy

- A previously cited article noted that about 70% of children with ADHD and epilepsy will benefit from standard treatment, such as methylphenidate.
- To date, there appears to be no firm evidence that the usual treatments for ADHD are likely to exacerbate seizures.

Besag, et al., 2016b

Pharmacotherapy of Psychopathology in Epilepsy

- Although studies of treatments for depression and anxiety, in populations with epilepsy, are limited, another article cited previously commented that SSRIs and cognitive behavioral therapy (CBT) are currently accepted treatments.
- The SSRIs and the SNRIs do not reduce seizure threshold, and may even lessen the chance of seizures.

Dunn, et al., 2016

Pharmacotherapy of Psychopathology in Epilepsy

- The AED pregabalin has been recommended as a first-choice treatment for generalized anxiety disorder in adults with epilepsy, but no data exists for treatment of children with anxiety and epilepsy.

Mula, 2016

Pharmacotherapy of Psychopathology in Epilepsy

- If psychosis is not drug-induced and requires antipsychotic treatment, it should not normally be withheld on the basis of possible seizure exacerbation (see the last section of this presentation).
- For postictal psychosis, the antipsychotic treatment can be withdrawn slowly when the psychotic features have resolved, but further antipsychotic treatment might be required if there are future episodes.

Besag, et al., 2016a

Pharmacotherapy of Psychopathology in Epilepsy

- Psychosis in association with the prescription of some antiepileptic drugs can also occur in children and adolescents.
- If the psychosis is drug-induced, a review of the antiepileptic medication is indicated. (see the last section of this presentation).

Besag, et al., 2016a

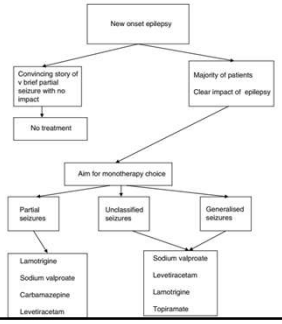
Pharmacotherapy of Combined IDD, MI and Epilepsy

Pharmacotherapy of Combined IDD, MI and Epilepsy

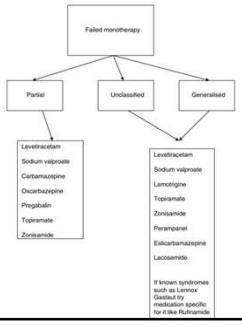
- There are no studies that specifically address the treatment of individuals with this clinical triad.
- Some experts have made recommendations for AED selections in those with IDDs and epilepsy.
- Given that several AEDs are also used to treat psychiatric disorders, suggested AEDs can be considered as first or second choices to treat epilepsy and some comorbid psychiatric disorders in individuals with IDDs:

Shankar, et al., 2016

Making a treatment choice: initial treatment



Making a choice: monotherapy failure



Pharmacotherapy of Combined IDD, MI and Epilepsy

- The use of AEDs is better-suited to treat bipolar disorder, less so for some anxiety and depressive disorders, and not for psychotic disorders (unless they derive from the epilepsy itself).
- Other classes of psychotropic medications can be used in individuals with the clinical triad, but must be used cautiously to avoid drug-drug interactions and other adverse effects.

Potential Adverse Events, Drug-Drug Interactions, and Proconvulsant Effects in the Treatment of Comorbid Disorders

Adverse Events

- The previously cited ILAE task force reported on adverse cognitive and behavioral effects of AEDs in children.
- They distinguished the older AEDs from the newer, and newest, AEDs.
- A striking finding was the lack of information on children.

Aldenkamp, et al., 2016

Adverse Events

- The authors surmised that there may be negative *cognitive* effects with phenobarbital, phenytoin, topiramate and zonisamide.
- Adverse *behavioral* effects were associated with phenobarbital, valproate, gabapentin, topiramate, levetiracetam and zonisamide.

Aldenkamp, et al., 2016

Adverse Events

- With regard to *cognitive* effects, valproate, carbamazepine (CBZ), gabapentin and oxcarbazepine appear to be neutral.
- CBZ appears to be neutral with regard to *behavioral* effects.
- Positive *cognitive* effects have been reported with lamotrigine (LTG) and levetiracetam.
- Positive *behavioral* effects have been reported with LTG.

Aldenkamp, et al., 2016

Adverse Events

- Although the data on adolescents with psychosis is somewhat limited, there seems every reason to recommend starting at low doses and escalating the dose slowly when AEDs that have a documented association with psychosis, such as vigabatrin and topiramate, are being prescribed.

Besag, et al., 2016a

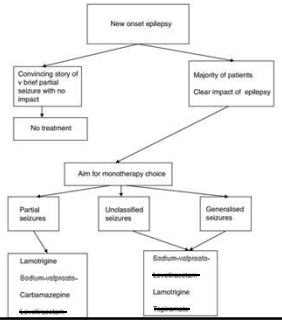
Recommendations for use of antiepileptic drugs in children, based on cognitive and behavioral complications

	Caution cognition[1]	**Caution behaviour**[1]	***Inconclusive/ lack of data***	**Neutral cognition**[1]	**Neutral behaviour**[3]	**Positive cognitive effects**	**Positive behavioural effects**
Older AEDs	**Phenobarbital Phenytoin**	**Phenobarbital Valproate**	*Ethosuximide Clobazam*	Valproate Carbamazepine	Carbamazepine		
Newer AEDs	**Topiramate**	**Gabapentin Topiramate Levetiracetam**	*Vigabatrin Felbamate Tiagabine*	Gabapentin Oxcarbazepine		Lamotrigine Levetiracetam	Lamotrigine
Newest AEDs	**Zonisamide**	**Zonisamide**	*Pregabalin ~~Stiripentol~~ Rufinamide Lacosamide ~~Retigabine~~*				

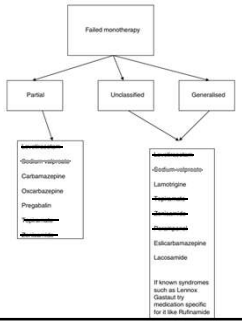
Note: Lined-out drugs not available in the US

Aldenkamp, et al., 2016

Making a choice: Considering adverse events



Making a choice: Considering adverse events



Adverse Events

- A study that evaluated the use of the newer AED perampanel in patients with ID and epilepsy found that behavioral adverse effects were present in 40.3%. Most common were aggression, agitated behavior, disruptive behavior, and mood symptoms.

Snoeijen-Schouwenaars, et al., 2017

AED, antidepressant, and antipsychotic drug-drug interactions

	TCA's	SSRI/SNRI	Atypical antidepressants	Antipsychotics
Carbamazepine	↑ TCA metabolism, except clomipramine ↑ Clomipramine serum concentration	↓ Carbamazepine metabolism ↑ SSRI metabolism	↓ Nefazodone serum concentration ↓ Vilazodone serum concentration Nefazodone: ↑ Carbamazepine serum concentration ↓ Carbamazepine epoxide metabolite	↓ Aripiprazole, brexpiprazole, cariprazine, lurasidone, paliperidone, quetiapine, risperidone, and ziprasidone serum concentration ↑ Clozapine myelosuppressive effect Quetiapine: ↑ Carbamazepine epoxide metabolite
Phenytoin		Fluoxetine, fluvoxamine, and sertraline: ↑ Phenytoin serum concentrations	↓ Trazodone, vilazodone serum concentration Trazodone: ↑ Phenytoin serum concentration Vilazodone: ↓ Phenytoin serum concentration	↓ Aripiprazole, brexpiprazole, cariprazine, clozapine, lurasidone, paliperidone, and quetiapine serum concentrations
Lamotrigine			↑ Mirtazapine CNS depressant effect	↑ Olanzapine sedative effects
Oxcarbazepine				↓ Aripiprazole serum concentrations
Zonisamide			↑ Mirtazapine CNS depressant effect	
Rufinamide				↓ Aripiprazole serum concentrations
Eslicarbazepine		↑ Citalopram serum concentration	↑ Mirtazapine CNS depressant effect	↓ Aripiprazole serum concentrations
Phenobarbital			↓ Vilazodone serum concentration	↓ Aripiprazole, brexpiprazole, cariprazine, clozapine, lurasidone, and quetiapine serum concentrations

Habibi, et al., 2016

AED, antidepressant, and antipsychotic drug-drug interactions

	TCA's	SSRI/SNRI	Atypical antidepressants	Antipsychotics
Tiagabine			↑ Mirtazapine CNS depressant effect	
Vigabatrin			↑ Mirtazapine CNS depressant effect	
Clobazam			↑ Mirtazapine CNS depressant effect	↓ Aripiprazole serum concentrations ↑ Brexpiprazole serum concentrations ↑ Clozapine adverse/toxic effects IM Olanzapine: ↑ Clobazam adverse/toxic effect
Valproate				↓ Olanzapine serum concentration ↑ Paliperidone serum concentration ↑ Risperidone adverse/toxic effects
Felbamate			↑ Mirtazapine CNS depressant effect	
Topiramate	↑ Amitriptyline CNS depressant effect, ↑ serum concentration		↑ Mirtazapine CNS depressant effect	
Gabapentin			↑ Mirtazapine CNS depressant effect	
Levetiracetam			↑ Mirtazapine CNS depressant effect	
Pregabalin			↑ Mirtazapine CNS depressant effect	
Ezogabine			↑ Mirtazapine CNS depressant effect	

Habibi, et al., 2016

AED and antipsychotic drug-drug interactions

	ARI	ASP	BRX	CAR	CLZ	ILO	LUR	OLZ	PAL	QUE	RIS	ZIP
ACZ	X	↕	X	↑	X	X	X	X	↕	↕	X	↕
BRV	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
CBZ	* o		*	↑*	*m s		*	*	*	*	*	*
CLB	*		*	↑	c		*					
DVX				↑								
ESL	*		*	↑	s		*			*		
ESX				↑	↑b							
EZG		↕		↑	u	↕		u	↕			↕
FOS	*	X	*	↑*	*	X	*	X	*	*	*	X
FLB	*	X	*	↑	X	X	*	X	X	X	X	X
GAB				↑								
LAC	X	X	X	↑	X	X	X	X	X	X	X	X
LAM		X		↑	X	X	X	X	X	X	X	X
LEV	X	X	X	↑	X	X	X	X	X	X	X	X
MTH				↑								
OXC	*		*	↑	*		*	*		*	*	*
PER	*		*	↑			*			*		
PRE				↑								
PHN	*	X	*	↑*	*	X	*	X	*		*	X
RUF	*		*	↑			*					
TIG	↑	↑	↑	↑		↑	↑	↑	↑	↑	↑	↑
TOP	*		*	↑			*					
VIG				↑								
ZON				↑	↑h			h				h

(Derived from Epocrates)

AED and antipsychotic drug-drug interactions

Abbreviations for antipsychotics (very top row):

ARI= aripiprazole	ASP= asenapine	BRX= brexpiprazole	CAR= cariprazine
CLZ= clozapine	ILO= iloperidone	LUR= lurasidone	OLZ= olanzapine
PAL= paliperidone	QUE= quetiapine	RIS= risperidone	ZIP= ziprasidone

Abbreviations for anticonvulsants (far left column):

ACZ= acetazolamide	BRV= brivaracetam	CBZ= carbamazepine	CLB= clobazam
DVX= divalproex	ESL= eslicarbazine	ESX= ethosuximide	EZG= ezogabine
FOS= fosphenytoin	FLB= felbamate	GAB= gabapentin	LAC= lacosamide
LAM= lamotrigine	LEV= levetiracetam	MTH= methsuximide	OXC= oxcarbazepine
PER= perampanel	PRE= pregabalin	PHN= phenytoin	RUF= rufinamide
TIG= tiagabine	TOP= topiramate	VIG= vigabatrin	ZON= zonisamide

Abbreviations/symbols for adverse effects:

***** = may decrease antipsychotic level. **m**= bone marrow toxicity. **b**= blood dyscrasias.
† = may alter seizure control/increase seizure risk. **s**= SIADH and/or hyponatremia.
u= urinary retention. **‡** = combo may incr. risk of QT prolongation, cardiac arrhythmias.
h= combo w/ drugs possessing anticholinergic effects may incr. risk of oligohidrosis, hyperthermia, and heat stroke **c**= cardiorespiratory arrest/collapse
o= orthostatic hypotension **X** = no significant side effects.

(Derived from Epocrates)

Proconvulsant Effects: Antipsychotics

Incidence Rate of Seizure by Antipsychotic Drug

Drug	No. of Patients	Person-Years	No. of Events	Incidence Rate[a]	95% Confidence Interval
Overall	288,397	57,562	550	9.6	8.8–10.4
Class					
FGAs	82,104	11,910	160	13.4	11.4–15.7
SGAs	206,293	46,523	390	8.4	7.6–9.3
Drug					
~~Amisulpride~~	~~5,653~~	~~1,320~~	~~16~~	~~12.1~~	~~6.9–19.7~~
Aripiprazole	7,118	1,784	7	3.9	1.6–8.1
Chlorpromazine	8,922	1,537	17	11.1	6.4–17.7
~~Chlorprothixene~~	~~782~~	~~172~~	~~6~~	~~34.9~~	~~12.8–75.9~~
~~Clothiapine~~	~~2,588~~	~~602~~	~~5~~	~~8.3~~	~~2.9–19.3~~
Clozapine	2,536	972	13	13.4	7.1–22.9
~~Flupentixol~~	~~2,559~~	~~774~~	~~6~~	~~7.8~~	~~2.9–16.9~~
Haloperidol	16,656	3,135	53	16.9	12.7–22.1
Olanzapine	9,126	2,218	12	5.4	2.8–9.4
Paliperidone	748	192	1	5.2	0.1–29.0
Perphenazine	455	52	1	19.3	0.5–107.6
Prochlorperazine	37,627	3,656	40	10.9	7.8–14.9
Quetiapine	35,446	9,612	84	8.7	7.0–10.8
Risperidone	31,089	7,835	56	7.1	5.4–9.3
~~Sulpiride~~	~~109,971~~	~~21,234~~	~~165~~	~~7.8~~	~~6.7–9.2~~
Thioridazine	4,743	970	25	25.8	16.7–38.0
Trifluoperazine	6,010	813	7	8.6	3.5–17.7
Ziprasidone	891	185	1	5.4	0.1–30.0
~~Zotepine~~	~~4,113~~	~~871~~	~~15~~	~~17.2~~	~~9.6–28.4~~

[a]Per 1,000 person-years.

Wu, et al., 2016

Proconvulsant Effects: Antipsychotics

Multivariate Cox Proportional Hazards Regression Model for Risk of Antipsychotic-Related Seizure

	Hazard Ratio (95% CI)	*P* Value
Age		
15–39 y	1.00	
40–64 y	0.74 (0.61–0.90)	.002
≥65 y	0.80 (0.57–1.12)	.200
Gender, male	1.34 (1.12–1.60)	.002
Psychiatric disorders		
Schizophrenia	1.71 (1.24–2.36)	.001
Bipolar disorder	1.24 (0.84–1.82)	.287
Major depressive disorder	0.94 (0.69–1.28)	.695
Mental retardation	1.95 (1.31–2.90)	.001
Autism spectrum disorder	1.97 (0.86–4.51)	.107
Alcohol use disorder	2.65 (1.98–3.56)	<.001
Substance use disorder	1.31 (0.93–1.85)	.120
Medical comorbidity		
Headache	1.02 (0.81–1.27)	.886
Cancer	1.35 (0.87–2.08)	.179
Hypertension	1.13 (0.86–1.48)	.392
Diabetes mellitus	1.12 (0.81–1.55)	.502
Dyslipidemia	0.75 (0.52–1.06)	.102
Chronic pulmonary disease	0.73 (0.52–1.01)	.061
Chronic renal failure	1.81 (1.07–3.05)	.026
Concomitant medication use		
Anticholinergics	1.42 (1.14–1.77)	.001
Antidepressants		
TCAs	1.12 (0.90–1.41)	.311
SSRIs	1.47 (1.21–1.80)	<.001
Other antidepressant	0.83 (0.67–1.02)	.077
Antiepileptics		
NTAEs	1.71 (1.37–2.14)	<.001
Other antiepileptics	5.31 (4.02–7.02)	<.001
Benzodiazepine	1.03 (0.80–1.33)	.801
Lithium	0.45 (0.24–0.85)	.014

Wu, et al., 2016

Proconvulsant Effects: Antidepressants

Antidepressant drug classes	Drug examples	Drugs with propensity to cause seizures and metabolic pathway
Nonselective monoamine reuptake inhibitors (TCA)	Amitriptyline, doxepin, nortriptyline, trimipramine	*Clomipramine* (CYP1A2, 3A4, 2D6)
Selective serotonin reuptake inhibitors (SSRI)	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	*None*
Selective noradrenaline or noradrenaline/serotonin reuptake inhibitors (SNRI)	Venlafaxine, reboxetine, duloxetine	*None*
Monoamine oxidase inhibitors (MAO), nonselective		*Maprotiline* (CYP2D6), *amoxapine* (CYP2D6)
Monoamine oxidase A inhibitors (MAO_A)	Moclobemide	*None*
Other antidepressants	Mianserin, mirtazapine	*Bupropion* (CYP2B6), inhibitor of CYP2D6

Johannessen Landmark, et al., 2016

Conclusions

- Individuals with combined IDDs, epilepsy and psychiatric disorders are complex and difficult to treat.
- AEDs can have adverse cognitive and behavioral effects.
- Some psychotropic medications can increase the risk of seizure activity.

Conclusions

- There are no medications that treat the underlying, core features of IDDs, so the focus of treatment is controlling seizure activity and reducing psychiatric symptoms.
- Initial treatment should target the most distressing and/or impairing symptoms.
- Use of medications should follow the “start low, go slow” approach.

Conclusions

- Try to use the least number of medications, choosing agents that can serve more than one function, e.g., AEDs that are also good mood stabilizers.
- It is a safe assumption that any clinical deterioration in patients on medications could be from the medications themselves, including side effects (e.g., constipation or urinary retention).

Questions?

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