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Table e-1: Prognosis: Risk of seizure recurrence after an unprovoked first seizure in adults (Class I and II studies)

Reference	Class	Design	Data collection	Concealed allocation	Completion rate	Spectrum bias	Outcome assessment	Comments
Hauser, 1982, ¹⁰ 1990 ¹¹	I	Prospective; representative cohort including both patients treated with AEDs and patients untreated with AEDs	238 patients; over 75% adults; patients with unprovoked first seizures	Yes; but choice of which AED to treat with was left to treating physicians	Over 85%	No	Outcome was seizure recurrence over up to 12 years. Objectively assessed at up to 3 years	Cohort included both treated and untreated patients depending on preference of referring or study physicians
First Seizure Trial Group 1993, ¹² 1997 ¹³	I	Prospective; representative cohort including equal numbers of patients treated with AEDs and patients untreated with AEDs	397 patients; over 70% adults; patients with unprovoked first seizures	Yes; but choice of which AED to treat with was left to treating physicians	Over 85%	No	Outcome was seizure recurrence over up to 12 years. Objectively assessed	Randomized, controlled trial of immediate AED treatment over the short term and long term
Das, 2000 ¹⁸	II	Prospective; representative cohort including both patients treated with AEDs and patients untreated with AEDs	Predominantly adult unprovoked first seizure patients	Yes	Over 80% completed 1 year of the study	No	Outcome was seizure recurrence at 12 and 24 mos. Objectively assessed	Cohort included many children (ages not clearly noted). Completion rate at 24 mos not provided
Bora, 1995 ¹⁷	II	Prospective;	147 adult GTC	No; some	All followed at	No	Outcome was seizure	Cohort included both

		representative cohort including both patients treated with AEDs and patients untreated with AEDs	unprovoked first seizure patients	patients treated with AEDs prior to entering study	least 6 months		recurrence at up to 4 years. Not clear how objectively well assessed	treated and untreated patients depending on preference of referring or study physicians. Completion rate high but not well described
Hopkins, 1988 ¹⁶	II	Prospective; representative cohort including both patients treated with AEDs and patients untreated with AEDs	306 over 80% adults; some patients with apparent provoked seizures	Yes; but choice of which AED to treat with was left to treating physicians	Not clearly specified but appears over 80%	No	Outcome was seizure recurrence at up to 3 years. Not clear how objectively well assessed	Cohort included both patients with provoked seizures and patients with unprovoked seizures. Treatment with AEDs was the choice of the referring physicians
Annegers, 1986 ¹⁹	II	Retrospective; representative cohort including both patients treated with AEDs and patients untreated with AEDs	424 patient with over 60% adults; unprovoked first seizure patients	No, retrospective study	Over 90% follow-up at 2 years	No	Outcome was objective	Retrospective representative cohort study following patient up to 10 years
Kho, 2006 ²⁰	II	Prospective; representative cohort including both patients treated with AEDs and patients untreated with AEDs	497 adult patients with both provoked and unprovoked first seizures	Yes; but choice of which AED to treat with was left to treating physicians	All followed for at least 1 year	No	Outcome was objective	Both patients with provoked seizures and patients with unprovoked seizures. Study focused mainly on comparison of multiple versus single seizures at presentation

Marson, 2005 ¹⁵	II	Prospective; somewhat representative cohort	Includes over 40% with more than 1 seizure on entry, and over 60% adults	Yes; randomized to immediate or deferred treatment; but choice of which AED to treat with was left to treating physicians	Over 90% follow-up at 1 year	No	Outcome was seizure recurrence based on questionnaire	Cohort includes over 40% with more than one seizure on entry and children. Outcomes based on patient questionnaire
Chandra, 1992 ²¹	II	Prospective; somewhat representative cohort from an individual practice	Adult patients with unprovoked first seizure referred to a practice in Indonesia	Yes	Follow-up in over 96% at 1 year	No	Outcome was seizure recurrence. Not clear how objectively well assessed	Patients with unprovoked first seizure referred to a practice in Indonesia
Gilad, 1996 ²²	II	Prospective; representative cohort from a hospital practice	Adult patients with mainly unprovoked and possibly some provoked first seizures	Yes	Follow-up in over 90% at 3 years	No	Outcome was seizure recurrence at 3 years. Not clear how objectively well assessed	Adult patients with mainly unprovoked and possibly some provoked first seizures referred to a hospital practice then randomized to immediate AED treatment or not

AED = antiepileptic drug; GTC = generalized tonic-clonic; RCT = randomized, controlled trial.

Table e-2: Therapeutics: Rates for short-term (1 and 2 years) seizure recurrence after an unprovoked first seizure in adults by immediate AED treatment (Class I and II studies)

Reference	Class	Design	Data collection	Concealed allocation	Completion rate	Intent-to-treat analysis	Outcome assessment	Comments
First Seizure Trial Group 1993, ¹² 1997 ¹³	I	Prospective; randomized representative cohort including equal numbers of AED treated and untreated patients	397 patients; over 70% adults; patients with unprovoked first seizures	Yes; but choice of which AED to treat with was left to treating physicians	Over 85%	Yes	Outcome was seizure recurrence and objective	RCT of immediate AED treatment over the short term and long term
Das, 2000 ¹⁸	II	Prospective; RCT, representative cohort, immediate AED treatment or no treatment	Predominantly adult patients with unprovoked first seizures seen at a single medical center	Yes	Over 80% completed 1 year of the study	Yes	Outcome was seizure recurrence. Not clear how objectively well assessed	Cohort included many children (ages not clearly noted). Completion rate at 24 mos. not provided
Marson, 2005 ¹⁵	II	Prospective; RCT of immediate vs delayed AED treatment; somewhat representative cohort, including patients with not just 1 seizure but prior also seizures	Includes over 40% with more than 1 seizure on entry, and over 60% adults	Yes; but choice of which AED to treat with was left to treating physicians	Over 90% follow-up at 1 year	Yes	Outcome was seizure recurrence based on patient questionnaire	Cohort includes over 40% with more than 1 seizure on entry and children. Outcomes based on patient questionnaire

Chandra, 1992 ²¹	II	Prospective; RCT; somewhat representative cohort from an individual practice	Adult patients with unprovoked first seizure referred to a practice in Indonesia randomized to receive valproate or placebo	Yes	Follow-up in over 96% at 1 year	Not clearly stated	Outcome was seizure recurrence. Not clear how objectively well assessed	Patients with unprovoked first seizures referred to a practice and randomized to receive valproate or placebo
Gilad, 1996 ²²	II	Prospective; representative cohort from a hospital practice; randomized to receive carbamazepine or no AED	Adult patients with mainly unprovoked and possibly some provoked first seizures	Yes	Follow-up in over 90% at 3 years	No	Outcome was seizure recurrence at 3 years. Not clear how objectively well assessed	Adult patients with mainly unprovoked and possibly some provoked first seizures referred to a hospital practice and then randomized to immediate AED treatment with carbamazepine or no AED

AED = antiepileptic drug; RCT = randomized, controlled trial.

Table e-3: Therapeutic: Rates of 2-year seizure remission over the longer term (> 3 years), comparing immediate to deferred AED treatment of an unprovoked first seizure in adults (Class I and II studies)

Reference	Class	Design	Data collection	Concealed allocation	Completion rate	Intent-to-treat analysis	Outcome assessment	Comments
First Seizure Trial Group 1993, ¹² 1997 ¹³	I	Prospective; randomized representative cohort including equal numbers of AED treated and untreated patients	397 patients; over 70% adults; patients with unprovoked first seizures	Yes; but choice of which AED to treat with was left to treating physicians	Over 85%	Yes	Outcome was based on achieving a 2-year seizure remission rate and objective	RCT of immediate AED as compared with delayed treatment over the short term and long term
Marson, 2005 ¹⁵	II	Prospective; RCT of immediate vs delayed AED treatment; somewhat representative cohort, including patients with not just 1 seizure but also prior seizures	Includes over 40% with more than 1 seizure on entry, and over 60% adults	Yes; but choice of which AED to treat with was left to treating physicians	Over 90% follow-up at 1 year	Yes	Major outcome was achieving a 2-year seizure remission and based on patient questionnaire	Cohort includes over 40% with more than 1 seizure on entry and children. Outcomes based on patient questionnaire

AED = antiepileptic drug; RCT = randomized, controlled trial.

Table e-4: Therapeutics: Risk of adverse events or side effects in adults with an unprovoked first seizure treated with AEDs

Reference	Class	Design	Data collection	Concealed allocation	Completion rate	Intent-to-treat analysis	Outcome assessment	Comments
First Seizure Trial Group 1993 ¹²	II	Prospective; randomized representative cohort including equal numbers of AED treated and untreated patients	397 patients; over 70% adults; patients with unprovoked first seizure; 20% discontinued AEDs at some point; side effects in untreated patients not considered	Yes; but choice of which AED to treat with was left to treating physicians	Over 85%; but 20% discontinued AEDs at some point, some due to side effects	Yes	Outcome was side effects from AEDs; AEDs included CBZ, PHT, PB, or SV	RCT of immediate AED treatment over the short and long term. 20% discontinued AEDs at some point either for side effects or other reasons; side effects in untreated patients not considered
Marson, 2005 ¹⁵	II	Prospective; RCT of immediate vs delayed AED treatment; somewhat representative cohort, including patients with not just 1 seizure but also prior seizures	Includes over 40% with more than one seizure on entry, and over 60% adults; side effects in untreated patients not considered	Yes; but choice of which AED to treat with was left to treating physicians	Over 90% follow-up at 1 year	Yes	Outcome side effects from AEDs; AEDS included CBZ, SV, PHT, or LMT	Cohort includes over 40% with more than 1 seizure on entry and children. Outcomes based on patient questionnaire; side effects in untreated patients not considered

Chandra, 1992 ²¹	II	Prospective; RCT; somewhat representative cohort from an individual practice	Adult patients with unprovoked first seizures referred to a practice in Indonesia randomized to receive valproate or placebo	Yes	Follow-up in over 96% at 1 year	Not clearly stated	Outcome side effects from AED, VPA	Patients with first unprovoked seizures from a neurology practice; randomized to valproate or placebo
Gilad, 1996 ²²	II	Prospective; representative cohort from a hospital practice; randomized to receive CBZ or no AED	Adult patients with mainly unprovoked and possibly some provoked first seizures; side effects in untreated patients not considered	Yes	Follow-up in over 90% at 3 years	No	Outcome side effects from AED, CBZ; not clear how objectively well assessed	Adult patients with mainly unprovoked and possibly some provoked first seizures referred to a hospital practice and then randomized to immediate AED treatment with CBZ or no AED; side effects in untreated patients not considered
Ruggles, 2001 ²⁷	III	Prospective; not representative cohort of elderly patients from a regional group practice	Adult elderly patients, over age 50 years; patients with unprovoked first seizure; side effects in untreated patients not considered	Yes; but choice of which AED to treat with was left to treating physicians	Follow-up in over 85% at 3 years	Not clearly stated	Outcome side effects from AED, PHT, CBZ, SV; not clear how objectively well assessed	Prospective; not representative cohort of elderly patients from a regional group practice; outcome side effects from AED, PHT, CBZ, SV; not clear how objectively well assessed

AED = antiepileptic drug; CBZ = carbamazepine; LMT = lamotrigine; PB = phenobarbital; PHT = phenytoin; RCT = randomized, controlled trial; SV = sodium valproate; VPA = valproic acid.

Table e-5. Risk of AEs in adults with an unprovoked first seizure treated with antiepileptic drugs

Reference	Class	No.	No. treated(%)	AED(s)	AEs treated, n(%)	AEs untreated, n(%)
12	II	397	204(51)	CBZ,PHT,PB, or VPA	14(7)	Not reported
15	II	1,443	722(50)	CBZ, VPA, PHT, or LMT	200(31)	Not reported
21	II	228	113(50)	VPA	10(9)	2(2)
22	II	87	45(52)	CBZ	9(20)	Not reported
28	III	48	42(88)	PHT, CBZ, VPA	13(27)	Not reported
Total		2,203	1,126(51)	CBZ, VPA, PHT,PB, or LMT	246(22)	Not adequately reported

AEs = adverse events; AED(s) = antiepileptic drug(s); CBZ = carbamazepine; LMT = lamotrigine; PB = phenobarbital; PHT = phenytoin; VPA = valproic acid.