Reference	Class	Design	Data	Concealed	Completion	Spectrum	Outcome	Comments
			collection	allocation	rate	bias	assessment	
Hauser, 1982, <sup>10</sup> 1990 <sup>11</sup>	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 to12 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, <sup>12</sup> 1997 <sup>13</sup>	Ι	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 to12 years. Objectively assessed	Randomized, controlled trial of immediate AED treatment over the short term and long term
Das, 2000 <sup>18</sup>	П	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 <sup>17</sup>	II	Prospective;	147 adult GTC	No; some	All followed at	No	Outcome was seizure	Cohort included both

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

		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 <sup>16</sup>	Π	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 patents with provoked seizures and patients with unprovoked seizures. Treatment with AEDs was the choice of the referring physicians
Annegers, 1986 <sup>19</sup>	П	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 <sup>20</sup>	Π	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 <sup>15</sup>	II	Prospective; somewhat representative cohort	Includes over 40% with more than 1 seizure on entry, and over	Yes; randomized to immediate or deferred treatment; but	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
			60% adults	choice of which AED to treat with was left to treating physicians				
Chandra, 1992 <sup>21</sup>	П	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 <sup>22</sup>	Π	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.

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Reference	Class	Design	Data collection	Concealed allocation	Completion rate	Intent-to- treat analysis	Outcome assessment	Comments
First Seizure	T	Prospective	397 natients:	Yes: but	Over 85%	Ves	Outcome was seizure	RCT of immediate AFD
Trial Group	1	randomized	over 70%	choice of	0.101 0.5 %	105	recurrence and	treatment over the short
1993 <sup>12</sup>		representative	adults: natients	which AFD			objective	term and long term
$1007^{13}$		cohort including	with	to treat with			objective	term and long term
1997		agual numbers of	unprovokod	was laft to				
		AED trasted and	first soizuros	troating				
		ALD iteated and	III St Seizures	nhysicians				
		notionto		physicians				
Dag. 200018	п	Prospective:	Prodominantly	Vas	Over 80%	Vas	Outcome was soizure	Cohort included many
Das, 2000	11	PCT	adult nationts	105	completed 1	105	rocurrence. Not clear	children (ages not clearly
		KCI,	with		completed 1		how objectively well	noted) Completion rate at
		aphort	with		year of the study		now objectively well	24 most provided
		immediate AED	finat acizumas				assesseu	24 mos. not provided
		immediate AED	first seizures					
		treatment or no	seen at a single					
	TT	treatment	medical center	X7 1 /	0.000/	X7		
Marson,	11	Prospective;	Includes over	Yes; but	Over 90%	Yes	Outcome was seizure	Cohort includes over 40%
200515		RCT of	40% with more	choice of	follow-up at 1		recurrence based on	with more than I seizure
		immediate vs	than 1 seizure	which AED	year		patient questionnaire	on entry and children.
		delayed AED	on entry, and	to treat with				Outcomes based on patient
		treatment;	over 60% adults	was left to				questionnaire
		somewhat		treating				
		representative		physicians				
		cohort, including						
		patients with not						
		just 1 seizure but						
		prior also						
		seizures						

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)

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

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

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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	Completion	Intent-to-	Outcome	Comments
				allocation	rate	treat analysis	assessment	
First Seizure	Ι	Prospective;	397 patients;	Yes; but	Over 85%	Yes	Outcome was based on	RCT of immediate AED as
Trial Group		randomized	over 70%	choice of			achieving a 2-year	compared with delayed
1993, <sup>12</sup>		representative	adults; patients	which AED			seizure remission rate	treatment over the short
1997 <sup>13</sup>		cohort including	with	to treat with			and objective	term and long term
		equal numbers of	unprovoked	was left to				
		AED treated and	first seizures	treating				
		untreated		physicians				
		patients						
Marson,	II	Prospective;	Includes over	Yes; but	Over 90%	Yes	Major outcome was	Cohort includes over 40%
200515		RCT of	40% with more	choice of	follow-up at 1		achieving a 2-year	with more than 1 seizure
		immediate vs	than 1 seizure	which AED	year		seizure remission and	on entry and children.
		delayed AED	on entry, and	to treat with			based on patient	Outcomes based on patient
		treatment;	over 60% adults	was left to			questionnaire	questionnaire
		somewhat		treating				
		representative		physicians				
		cohort, including						
		patients with not						
		just 1 seizure but						
		also prior						
		seizures						

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	Completion	Intent-to-	Outcome	Comments
				allocation	rate	treat analysis	assessment	
First Seizure	II	Prospective;	397 patients;	Yes; but	Over 85%; but	Yes	Outcome was side	RCT of immediate AED
Trial Group		randomized	over 70%	choice of	20%		effects from AEDs;	treatment over the short and
1993 <sup>12</sup>		representative	adults; patients	which AED	discontinued		AEDs included CBZ,	long term. 20%
		cohort including	with	to treat with	AEDs at some		PHT, PB, or SV	discontinued AEDs at some
		equal numbers of	unprovoked	was left to	point, some			point either for side effects
		AED treated and	first seizure;	treating	due to side			or other reasons; side effects
		untreated	20%	physicians	effects			in untreated patients not
		patients	discontinued					considered
			AEDs at some					
			point; side					
			effects in					
			untreated					
			patients not					
			considered					
Marson,	II	Prospective;	Includes over	Yes; but	Over 90%	Yes	Outcome side effects	Cohort includes over 40%
200515		RCT of	40% with more	choice of	follow-up at 1		from AEDs; AEDS	with more than 1 seizure on
		immediate vs	than one seizure	which AED	year		included CBZ, SV,	entry and children.
		delayed AED	on entry, and	to treat with			PHT, or LMT	Outcomes based on patient
		treatment;	over 60%	was left to				questionnaire; side effects in
		somewhat	adults; side	treating				untreated patients not
		representative	effects in	physicians				considered
		cohort, including	untreated					
		patients with not	patients not					
		just 1 seizure but	considered					
		also prior						
		seizures						

Chandra, 1992 <sup>21</sup>	П	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 <sup>22</sup>	Ш	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 <sup>27</sup>	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.

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			No.		AEs treated,	
Reference	Class	No.	treated(%)	AED(s)	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

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

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