

## Supplementary Material S1 Search strategy

**Schizophrenia:** Schizophrenia OR Schizophrenias OR Schizophrenic Disorders  
OR Disorder, Schizophrenic OR Disorders, Schizophrenic OR Schizophrenic Disorder OR  
Dementia Praecox OR Psychotic Disorders OR Schizophrenia OR Schizophren OR Psychosis  
OR Psychot

**Antipsychotics:** Antipsychotics OR Anti-psychotics OR Neuroleptics  
OR Acepromazine OR Acetophenazine OR Amisulpride OR Aripiprazole OR Asenapine OR  
Benperidol OR Blonanserin OR Bromperidol OR Butaperazine OR Carpipramine OR  
Chlorproethazine OR Chlorpromazine OR Chlorprothixene OR Clocapramine OR Clopenthixol  
OR Clothiapine OR Clotiapine OR Clozapine OR Cyamemazine OR Cyamepromazine OR  
Dixyrazine OR Droperidol OR Fluanisone OR Flupenthixol OR Flupentixol OR Fluphenazine  
OR Fluspirilen OR Fluspirilene OR Haloperidol OR Iloperidone OR Levomepromazine OR  
Levosulpiride OR Lithium OR Loxapine OR Lurasidone OR Melperone OR Mepazine OR  
Mesoridazine OR Methotrimeprazine OR Molindone OR Moperone OR Mosapramine OR  
Olanzapine OR Oxypertine OR Paliperidone OR Penfluridol OR Perazine OR Periciazine OR  
Pericyazine OR Perospirone OR Perphenazine OR Pimozide OR Pipamperone OR  
Pipothiazine OR Pipotiazine OR Prochlorperazine OR Promazine OR Promethazine OR  
Prothipendyl OR Quetiapine OR Remoxipiride OR Reserpine OR Risperdal OR Risperidone  
OR Seroquel OR Sertindole OR Stelazine OR Sulpiride OR Sultopride OR Thiopropazate OR  
Thiopropazine OR Thioridazine OR Tiospirone OR Thiothixene OR Tiapride OR Tiotixene  
OR Trifluoperazine OR Trifluoperidol OR Trifluoperidol OR Triflupromazine OR Trifluperazine  
OR Veralipride OR Ziprasidone OR Zotepine OR Zuclopenthixol

**Mortality:** Mortality OR Death OR Years of Life Lost OR Suicide OR Survival OR Survival  
Analysis OR Kaplan-Meier Estimate OR Suicide OR Suicide, Assisted OR Heart Arrest OR  
Cardiac Arrest OR Heart Attack OR Heart Arrest OR Cardiovascular Stroke

**Table S1** Basic characteristics of the included studies

Author (year)	Population diagnosis	Country and method of enrollment	Total sample size	Average follow-up time	Comparisons	Mean age (SD)	Male (%)
Randomized trials							
Alphs (2015) <sup>1</sup>	Schizophrenia (DSM) Outpatients	USA Recruitment	450	1.25 (2010-2013)	Paliperidone Other oral antipsychotics	37.7 (10.6) 38.6 (10.4)	193 (85.4) 190 (87.2)
Gaebel (2010) <sup>2</sup>	Schizophrenia 585	Multinational	711	2.00 (2004-2007)	Risperidone LAI	40.6 (12.5)	195 (59.3)
Arce (2012) <sup>3</sup>	Schizoaffective 126 (DSM) In- and outpatients	Recruitment			Quetiapine Aripiprazole	42.6 (13.1) 40.9 (12.9)	191 (56.7) 25 (55.6)
John (2020) <sup>4</sup>	Schizophrenia 234 (DSM)	USA Recruited from clinics	234	1.63 (2014-2019)	Aripiprazole LAI Clinician's choice	25.18 (4.3) 24.7 (4.1)	172 (73.5) 196 (76.9)
Matsumoto (2018) <sup>5</sup>	Schizophrenia 106 (DSM) Adolescents In- and outpatients	Japan NS	106	1.10 (2010-2014)	Aripiprazole	15.1 (1.4)	37 (54.4)
Meltzer (2003) <sup>6</sup>	Schizophrenia 62 Schizoaffective 38 (DSM) High risk suicide	Multinational Recruitment	980	2.00 (1998-2001)	Clozapine Olanzapine	37.1 (10.3) 37.0 (10.3)	301 (61.4) 301 (61.4)
Ritchie (2010) <sup>7</sup>	Schizophrenia 66 (NS) Old age	Australia Recruited from psychiatric treatment setting	66	3.50 (1997-2000)	Olanzapine Risperidone	69.9 (7.3) 69.7 (4.8)	10 (29.4) 9 (28.1)
Savitz (2015) <sup>8</sup>	Schizophrenia 400 (DSM) Adolescent	Multinational NS	400	2.00 (2007-2012)	Paliperidone	15.4 (1.6)	243 (61)
Savitz (2016) <sup>9</sup>	Schizophrenia 1,429 (DSM)	Multinational NS	1,429	1.35 (2012-2015)	Paliperidone	38.4 (11.9)	782 (55)

Thomas (2010) <sup>10</sup>	Schizophrenia 9,809 (NS)	Europe	9,809	1.40	Sertindole	37.1 <sup>†</sup>	2,710 (55.2)	
		Asia		(2002-2008)	Risperidone	37.1	2,716 (55.3)	
		Recruitment						
Zhang (2015) <sup>11</sup>	Schizophrenia 521 (DSM)	Asia-Pacific region	521	1.50	Paliperidone	28.7 (8.0)	341 (65.5)	
		Recruitment		(2010-2013)				
Cohort studies								
Chang (2020) <sup>12</sup>	Schizophrenia (ICD) Newly diagnosed	Korea	80,581	7.00 <sup>†</sup>	FGA only	35.2 (6.5) <sup>‡</sup>	40,789 (50.9) <sup>‡</sup>	
		Database		2004-2017	SGA only			
				Combined				
Cho (2019) <sup>13</sup>	Schizophrenia Schizoaffective Bipolar disorder (ICD) Treatment-resistant	UK	2,837	3.90	Clozapine	38.7 (11.4) <sup>‡</sup>	1,773 (62.5) <sup>‡</sup>	
		Database		(2007-2016)	Non-clozapine			
Christy (2018) <sup>14</sup>	schizophrenia Non-affective psychosis (DSM) first-episode	Hong Kong	178	10.00	Quetiapine	24.2 (6.4)	80 (45)	
		Medical records		(2003-2014)				
Cullen (2013) <sup>15</sup>	Schizophrenia 2,132 (ICD) Outpatients	USA	2,132	10.00	FGA	41.6 (10.1)	1,033 (51)	
		Database		(1994-2004)	Others			41.6 (10.1)
Davis (2014) <sup>16</sup>	Schizophrenia Schizoaffective (DSM) In- and outpatients	USA	320	NS	Clozapine	48 (0.6)	292 (91.3)	
		Database		(1993-2007)				
Deslandes (2015) <sup>17</sup>	Schizophrenia Schizoaffective (NS)	UK	176	5.00	Risperidone	41.2 (12.9)	58 (69)	
		Medical records		(2006-2013)	Aripiprazole			NS for total
Dickson (1998) <sup>18</sup>	Schizophrenia 26 (DSM) Treatment-resistant In- and outpatients	Canada	26	3.00	Continuers	31.8 <sup>‡</sup>	24 <sup>‡</sup> (92.3)	
		Clinical records		(NS)	Discontinuers			(22-68)
								Interrupted clozapine users

Enger (2004) <sup>19</sup>	Schizophrenia 1,920 (ICD) In- and outpatients	United States Database	1,1520	1.76 (1995-1999)	Atypical only Typical only Both	38.2 (14) <sup>‡</sup>	4,766 (41.3) <sup>‡</sup>
Gaertner (2000) <sup>20</sup>	Schizophrenia 23 (ICD) Outpatients	Germany NS	23	3.80 (1993-NS)	Clozapine	40 (13)	18 (78.2)
Girgis (2011) <sup>21</sup>	Schizophrenia 122 Schizophreniform 38 (DSM) First episode In- and outpatients	China Medical records	160	9.00 (1995-2007)	Clozapine Chlompromazine	28.7 (6.9) <sup>‡</sup>	84 (52.2) <sup>‡</sup>
Hayes (2015) <sup>22</sup>	Schizophrenia 9,437 Schizoaffective 805 Bipolar affective disorder 4,512 (ICD) In- and outpatients	UK Medical records	14,754 <sup>§</sup>	3.03 (2007-2011)	Clozapine Others Non-user	43.2 (16.1) <sup>§</sup>	7,985 (54.1) <sup>§</sup>
Hennessy (2002) <sup>23</sup>	Schizophrenia 124,718 (ICD) Outpatients	USA Database	12,4718	1.10 1993-1996	Clozapine Haloperidol Risperidone Thioridazine	NS	47,812 (50)
Joukamaa (2006) <sup>24</sup>	Schizophrenia (NS)	Finland Mini-Finland Health Survey	99	17.00 (1978-1994)	Polypharmacy Monotherapy No use	NS	46 (46.5)
Jihoon (2021) <sup>25</sup>	Schizophrenia 86,923 (ICD) In- and outpatients	Korea Database	86,923	5.86 <sup>†</sup> (2003-2017)	Olanzapine Risperidone Aripiprazole Quetiapine Untreated	45 (32-60) <sup>†</sup>	42,353 (48.7) <sup>‡</sup>
Kadra (2018) <sup>26</sup>	Schizophrenia 5,896 Schizoaffective 639 Bipolar disorder 1,886 (ICD)	UK Records	10,945	4.48 2007-2014	Monotherapy Polypharmacy	42.2 38.1	4,684 (55.6) 1,470 (58.2)

Kasper (2010) <sup>27</sup>	Schizophrenia 2,321	Europe	2,321	1.50	Sertindole	39 <sup>†</sup>	570 (54)
	(experience or clinical judgement)	Recruitment		(1997-1998)	Non-Sertindole	42 <sup>†</sup>	755 (60)
	Not currently treated						
Kelly (2010) <sup>28</sup>	Schizophrenia 964	USA	1,686	6-10 years	Clozapine	39 (9.8)	690 (64)
	Schizoaffective 561	Database		(1994-2004)	Risperidone	41.2 (11.7)	369 (61)
	Disorder psychosis NOS 161 (DSM)						
	In- and outpatients						
Khan (2017) <sup>29</sup>	Schizophrenia 503	Australia	503	9.00	Clozapine	44 (12)	397 (78.9)
	Treatment-resistant (NS)	NS		(2009-2015)			
	Outpatients						
Lee (2015) <sup>30</sup>	Schizophrenia 75	Canada	94	1.40	Clozapine	35.9	68 (72.3)
	Schizoaffective 17	Database		(2009-2010)			
	Bipolar disorder 1 (NS)						
Lindstrom (1989) <sup>31</sup>	Schizophrenia 89	Sweden	96	12.50	Clozapine	36.1	64 (66.7)
	Schizoaffective 7	Recruited from clinic		(1974-1986)			
	(ICD)						
	In- and outpatients						
Modai (2000) <sup>32</sup>	Schizophrenia (ICD)	Israel	5,479	6.70	Clozapine	67.4 <sup>‡</sup>	NS
	Treatment resistant	Medical records		(1991-1997)	Non-clozapine		
	Inpatients						
Montout (2002) <sup>33</sup>	Schizophrenia 3,325 (ICD)	France	3,325	4.00	Phenothiazines	39.3 <sup>‡</sup>	2,127 (64) <sup>‡</sup>
	In- and outpatients	Recruited from psychiatric sectors		(1993-1997)	Butyrophenones		
					Benzamides		
					Thioxanthenes		
Munro (1999) <sup>34</sup>	Schizophrenia (NS)	UK	12,720	8.00	Clozapine	36.8	8,533 (67)
	Treatment-resistant	Ireland		(1990-1997)			
		Database					

Patrick (2020) <sup>35</sup>	Schizophrenia 646 Schizoaffective 400 Disorder psychosis NOS 153 (DSM) Inpatients	USA Patient records	1,199	20.00 (1994-2014)	Risperidone OR Clozapine	41 (11.4)	745 (62)
Pridan (2015) <sup>36</sup>	Schizophrenia 527 (DSM) (elderly) Inpatients	Israel Medical records	527	5.00 (2007-2012)	Clozapine Others	67.4 (7) <sup>‡</sup>	245 (46.5) <sup>‡</sup>
Ran (2015) <sup>37</sup>	Schizophrenia 510 (ICD)	China Epidemiological data	510	14.00 (1994-2008)	Treated Untreated	44.6 <sup>‡</sup>	237 (43.9) <sup>‡</sup>
Rimon (1994)	Schizophrenia 96 Schizoaffective 7 (DSM) In- and outpatients	Finland Medical records	103	3.40 NS	Clozapine	36.9	59 (57.3)
Schulte (2016) <sup>38</sup>	Schizophrenia 81 Schizoaffective 13 NS In- and outpatients	Netherlands Database	94	12.30 (1989-2010)	Clozapine Never treated with clozapine	39 (11) 40 (11)	74 (78.8) 73 (77.7)
Srivastava (2002) <sup>39</sup>	Schizophrenia 25 (ICD) Treatment resistant	India NS	25	3.00 (1994-1997)	Clozapine	NS	15(60)
Taipale (2018) <sup>40</sup>	Schizophrenia Schizoaffective (ICD) Chronic patients First-episode In- and outpatients	Sweden Database	29,823	5.70 (2006-2014)	FGA SGA Non-user	44.9 (16-64)	16,999 (57)
Taipale (2020) <sup>41</sup>	Schizophrenia (ICD) Prevalent cohort 62,250 First-episode patients: 8,719 In- and outpatients	Finland Database	70,969	14.10 <sup>†</sup> (1996-2015)	Antipsychotics Non-user	46.8 41.2	31,250 (50.2) 4,900 (56.2)

Taub (2020) <sup>42</sup>	Schizophrenia 1,817 (ICD) In and out-patients	Israel Database	1,817	3.00 (2012-2014)	Clozapine	43.7 (13)	1,157 (63.7)
Tenback (2012) <sup>43</sup>	Schizophrenia 7,415 (DSM) In- and outpatients	Netherland Database	10,5141	3.00 (2006-2008)	User Non-user	45.5 (13.9) 39.9 (22.7)	4,538 (61.2) 45,931(47)
Tiihonen (2009) <sup>44</sup>	Schizophrenia 66,681 (ICD) Outpatients	Finland Database	66,681	7.80 (1996-2006)	Antipsychotics Non-user	51 <sup>‡</sup>	30,803 (46) <sup>‡</sup>
Ward (2006) <sup>45</sup>	Schizophrenia 45,045 (ICD)	Canada Database	45,045	3.10 <sup>¶</sup> (1999-2003)	Risperidone Olanzapine Quetiapine	NS	23,528 (52.2) <sup>‡</sup>
Weitoft (2014) <sup>46</sup>	Schizophrenia Schizoaffective (ICD) In- and outpatients	Sweden Database	26,046	6.00 (2006-2011)	Antipsychotics Non-user	48.4 <sup>‡</sup>	14,397 (55.3) <sup>‡</sup>
Wimberley (2017) <sup>47</sup>	Schizophrenia (ICD) Treatment-resistant In- and outpatients	Denmark Database	2,370	6.80 <sup>†</sup> (1996-2013)	Clozapine Others Non-user	30.1 <sup>†</sup>	1,284 (54.2) <sup>‡</sup>
Zalm (2020) <sup>48</sup>	Schizophrenia 23,627 Schizoaffective 2,926 disorder psychosis NOS 9,081 (ICD) Incidence-cohort Prevalence-cohort outpatients	Denmark Database	50,881	11.30 (1995-2013)	Clozapine Others	39.7 (16.5) <sup>†</sup>	28,290 (55.6) <sup>‡</sup>
Case-control studies							
Chen (2015) <sup>49</sup>	Schizophrenia (ICD) Newly diagnosis	China Taiwan Database	1,624	3.81 3.91 (1997-2008)	FGA SGA	38.61 (12.3) 38.34 (12.7)	970 (59.7)

Mela (2016) <sup>50</sup>	Psychotic disorder Related disorder Offenders Inpatients	Canada Medical records	98	2.00 (1984-2012)	Clozapine Non-clozapine	NS	94 (95.9) <sup>‡</sup>
Sernyak (2001) <sup>51</sup>	Schizophrenia 4,245 NS Inpatients	USA Database	4,245	6.00 (1992-1998)	Clozapine ever Clozapine never	43.04 (9.3) 43.6 (11.1)	NS
Taylor (2009) <sup>52</sup>	Schizophrenia 250 Schizoaffective 29 Disorder psychosis NOS 43 <sup>  </sup> NS	UK Database	779	4.67 2002-2006	Clozapine Risperidone	36.4 (11.6) 38.6 (13.8) <sup>  </sup>	NS

LAI = long-acting injection; NOS = not otherwise specified; NS = nonspecific.

† Only provided the median age and follow-up time.

‡ No detailed data for each group, only for of the entire sample.

§ Only patients with schizophrenia were included in our analysis.

|| Different follow-up times; we chose the longest.

¶ Diagnosis and mean age only specified for discontinuers.



**Table S2** Quality assessment of included studies with cohort and case-control studies

Study	Selection (out of 4 stars)	Comparability (out of 2 stars)	Outcome (out of 3 stars)	Total score (maximum 9)
Cohort studies				
Chang (2020)	****	**	**	8
Cho J (2019)	***	**	**	7
Christy (2018)	***	**	**	7
Cullen (2013)	****		***	7
Davis (2014)	**		**	4
Deslandes (2015)	***		**	5
Dickson (1998)	***		***	6
Enger (2004)	****	**	***	9
Gaertner (2000)	***		*	4
Girgis (2011)	****	**	**	8
Hayes (2015)	****	**	**	8
Hennessy (2002)	****	**	***	9
Jihoon (2021)	****	**	**	8
Joukamaa (2006)	****	**	**	8
Kadra G (2018)	****	**	***	9
Kasper (2010)	***		**	5
Kelly (2010)	***	**	**	7
Khan (2017)	***		***	6
Lee (2015)	***		**	5
Lindstro (1989)	**		***	5
Modai (2000)	****		**	6
Montout (2002)	****		*	5
Munro (1999)	***		**	5
Patrick (2020)	***		**	5
Pridan (2014)	***		***	6
Pridan (2015)	***		***	6
Ran (2015)	****		**	6
Rimon (1994)	***		**	5
Schulte (2016)	****	**	**	8
Srivastava (2002)	**		**	4
Taipale (2018)	****	**	***	9
Taipale (2020)	****	**	***	9
Taub (2020)	***	**	***	8
Tenback (2012)	****	**	**	8
Tiihonen (2009)	****	**	***	9
Ward (2006)	**		**	4
Weitofte (2014)	****	**	**	8
Wimberley (2017)	****	**	**	8

Zalm (2020)	****	**	***	9
Case-control studies				
Chen (2015)	****	**	**	8
Mela (2016)	***		*	4
Sernyak (2001)	****	**	**	8
Taylor (2009)	**	*	*	4

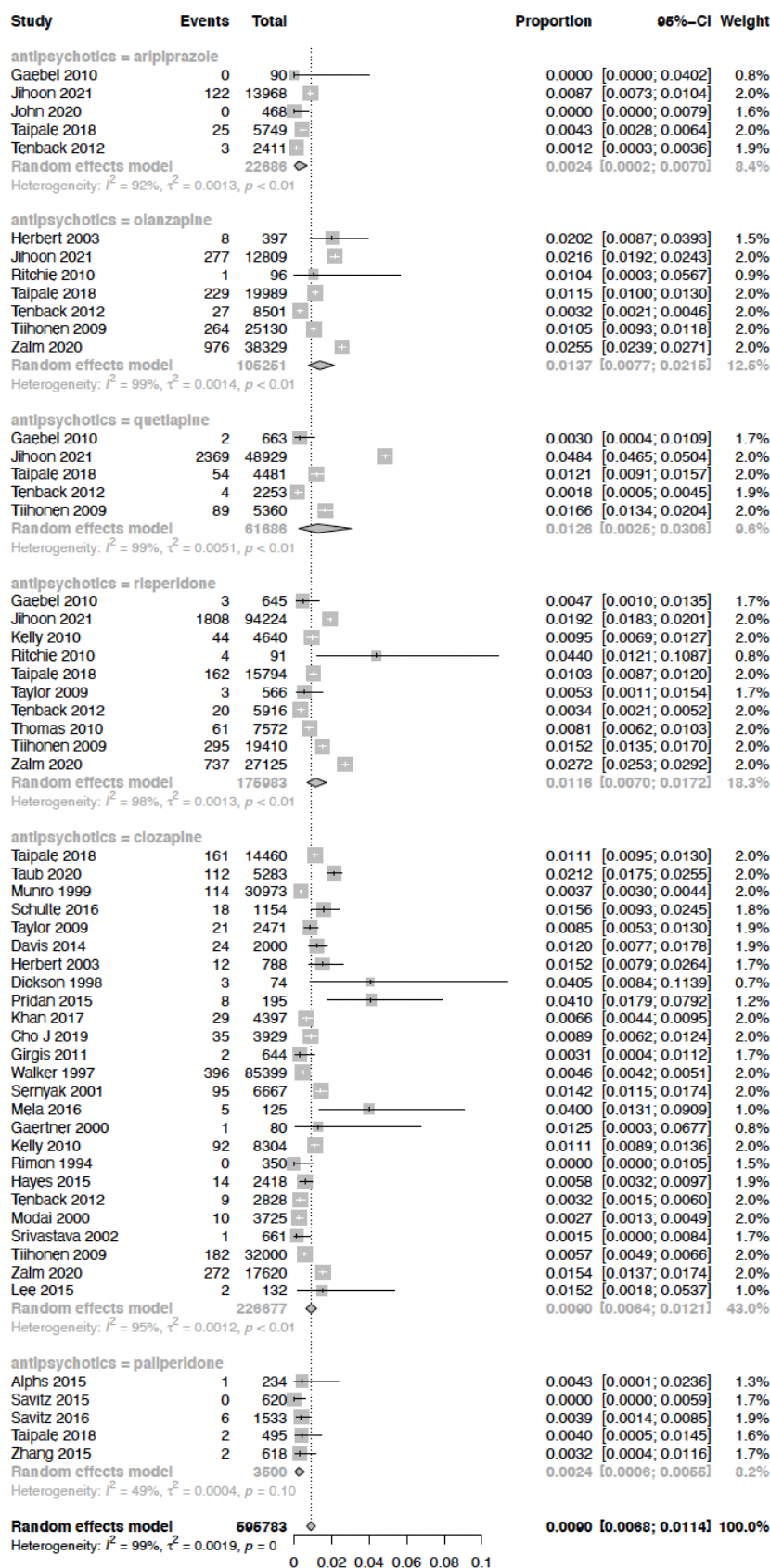
**Table S3** Meta-regression of the mortality of schizophrenia patients using antipsychotics

Variable	$\beta$	Se	95%CI		p-value
			Lower limit	Upper limit	
Follow-up time	0.0008	0.0011	-0.0014	0.0030	0.4534
Mean age	0.0018	0.0006	0.0007	0.0029	0.0010
Male (%)	-0.0001	0.0005	-0.0011	0.0009	0.8111
Sample size	0.0000	0.0000	-0.0000	0.0000	0.0609

**Figure S1** Quality assessment of included studies with randomized design

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Alphs 2015	+	+	+	+	+	+	+
Gaebel 2010	+	?	+	+	-	-	?
John M 2020	+	+	?	+	-	+	?
Matsumoto 2018	+	+	-	+	-	+	-
Meltzer 2003	+	?	-	+	+	-	?
Ritchie 2010	?	?	-	+	-	-	+
Savitz 2015	?	?	+	-	-	+	+
Savitz 2016	+	+	+	+	+	-	+
Thomas 2010	+	+	-	+	-	+	+
Zhang 2015	-	?	?	?	-	+	+

**Figure S2** Comparison of long-term death of schizophrenia using different antipsychotics



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