

Online Resource 1

The Impact of Antipsychotic Dose Reduction on Clinical Outcomes and Health Care Resource Use Among Medicare Patients With Schizophrenia

Miriam L. Zichlin, MPH¹; Fan Mu, MBBS, PhD¹; Sam Leo, PharmD²; Rajeev Ayyagari, PhD¹

¹Analysis Group, Inc., Boston, MA, USA; ²Teva Pharmaceuticals, Parsippany, NJ, USA.

Corresponding author:

Email: Rajeev.ayyagari@analysisgroup.com

Journal:

Clinical Drug Investigation

Caption:

Additional tables and figures that show baseline characteristics and outcomes for patients in the $\geq 10\%$ and $\geq 30\%$ dose reduction and stable dose cohorts, stratified by age (< 65 years and ≥ 65 years). A patient selection flow diagram is also included.

Table 1. Dose Distribution for Ten Most Frequently Used Antipsychotics During Stable Dose Period in the $\geq 10\%$ and $\geq 30\%$ Dose Reduction Cohorts (Full Population)

Drug	$\geq 10\%$ dose reduction cohorts		$\geq 30\%$ dose reduction cohorts	
	Dose reduction (n=276,030)	Stable dose (n=276,030)	Dose reduction (n=211,575)	Stable dose (n=211,575)
Risperidone, n (%)	63,307 (22.9)	60,804 (22.0)	50,141 (23.7)	46,689 (22.1)
Mean (SD) dose, mg	3.9 (2.5)	2.9 (2.2)	3.7 (2.5)	2.8 (2.2)
Quetiapine, n (%)	58,845 (21.3)	56,643 (20.5)	46,347 (21.9)	43,672 (20.6)
Mean (SD) dose, mg	400.8 (285.3)	271.4 (245.7)	383.3 (282.4)	268.2 (244.7)
Olanzapine, n (%)	49,276 (17.9)	45,828 (16.6)	37,304 (17.6)	34,926 (16.5)
Mean (SD) dose, mg	18.9 (10.0)	13.8 (8.6)	18.7 (10.5)	13.6 (8.6)
Aripiprazole, n (%)	23,415 (8.5)	36,037 (13.1)	18,572 (8.8)	27,397 (12.9)
Mean (SD) dose, mg	18.7 (10.4)	14.3 (10.0)	18.4 (10.8)	14.2 (9.9)
Clozapine, n (%)	21,690 (7.9)	10,617 (3.8)	12,688 (6.0)	8,002 (3.8)
Mean (SD) dose, mg	394.6 (184.1)	383.3 (190.3)	377.8 (186.5)	382.7 (189.3)
Ziprasidone, n (%)	14,406 (5.2)	13,348 (4.8)	10,930 (5.2)	10,133 (4.8)
Mean (SD) dose, mg	141.9 (61.5)	112.2 (56.7)	138.3 (63.7)	111.9 (56.6)
Haloperidol, n (%)	14,347 (5.2)	13,626 (4.9)	11,339 (5.4)	10,699 (5.1)
Mean (SD) dose, mg	13.7 (11.5)	9.9 (9.3)	13.3 (11.3)	9.9 (9.4)
Fluphenazine, n (%)	6,055 (2.2)	5,805 (2.1)	4,940 (2.3)	4,526 (2.1)
Mean (SD) dose, mg	17.4 (11.7)	12.5 (9.8)	16.8 (11.3)	12.4 (9.8)
Lurasidone, n (%)	5,578 (2.0)	10,143 (3.7)	4,485 (2.1)	7,657 (3.6)
Mean (SD) dose, mg	92.7 (39.6)	69.2 (37.8)	89.5 (39.4)	69.2 (37.9)

Paliperidone, n (%)	4,351 (1.6)	6,194 (2.2)	3,649 (1.7)	4,659 (2.2)
Mean (SD) dose, mg	9.0 (3.6)	7.2 (3.0)	8.5 (3.6)	7.2 (3.0)

SD, standard deviation.

Table 2. Baseline Demographics of ≥10% Dose Reduction Cohorts Stratified by Age

Characteristic	<65 Years		≥65 Years	
	Dose reduction (n=189,386)	Stable dose (n=189,386)	Dose reduction (n=86,644)	Stable dose (n=86,644)
Age, years, mean (SD) ^a	48.4 (10.6)	48.4 (10.6)	74.5 (7.7)	74.5 (7.8)
Schizophrenia duration, months, mean (SD) ^a	33.2 (21.3)	24.6 (21.7)	31.7 (21.5)	21.1 (21.0)
Sex, male, n (%)	106,758 (56.4)	106,758 (56.4)	30,576 (35.3)	30,576 (35.3)
Duration of follow-up, months, mean (SD) ^a	4.9 (6.9)	9.2 (8.8)	5.4 (7.0)	8.9 (8.4)
Index drug class, n (%)				
Typical antipsychotic	22,994 (12.1)	22,994 (12.1)	10,948 (12.6)	10,948 (12.6)
Atypical antipsychotic	166,392 (87.9)	166,392 (87.9)	75,696 (87.4)	75,696 (87.4)
Index year, n (%)				
2011	13,070 (6.9)	13,070 (6.9)	5,062 (5.8)	5,062 (5.8)
2012	29,313 (15.5)	29,313 (15.5)	12,835 (14.8)	12,835 (14.8)
2013	30,041 (15.9)	30,041 (15.9)	12,696 (14.7)	12,696 (14.7)
2014	30,033 (15.9)	30,033 (15.9)	12,773 (14.7)	12,773 (14.7)
2015	29,010 (15.3)	29,010 (15.3)	13,135 (15.2)	13,135 (15.2)
2016	29,028 (15.3)	29,028 (15.3)	14,182 (16.4)	14,182 (16.4)
2017	28,891 (15.3)	28,891 (15.3)	15,961 (18.4)	15,961 (18.4)
Comorbidity profile, n (%)				
Substance-related and addictive disorders ^a	61,457 (32.5)	70,715 (37.3)	11,051 (12.8)	13,908 (16.1)
Anxiety disorders ^a	50,410 (26.6)	57,210 (30.2)	25,183 (29.1)	29,042 (33.5)
Bipolar disorders ^a	62,700 (33.1)	67,997 (35.9)	21,631 (25.0)	22,416 (25.9)
Depressive disorders ^a	62,043 (32.8)	70,993 (37.5)	35,960 (41.5)	40,281 (46.5)
Personality disorders ^a	11,314 (6.0)	11,855 (6.3)	2,112 (2.4)	2,586 (3.0)

Schizophrenia-spectrum disorders (excluding schizophrenia) ^a	30,613 (16.2)	36,375 (19.2)	20,179 (23.3)	24,258 (28.0)
Sleep-wake disorders ^a	30,845 (16.3)	33,594 (17.7)	12,523 (14.5)	15,258 (17.6)
TD	1,386 (0.7) ^b	1,152 (0.6) ^b	1,392 (1.6)	1,336 (1.5)
Trauma- and stressor-related disorders ^a	16,396 (8.7)	18,665 (9.9)	3,613 (4.2)	4,615 (5.3)
Mean (SD) CCI score^a	0.9 (1.5)	1.0 (1.6)	2.2 (2.0)	2.3 (2.2)
AIDS/HIV, n (%) ^a	2,548 (1.3)	3,247 (1.7)	264 (0.3)	391 (0.5)
Cancer, n (%) ^a	5,044 (2.7)	5,474 (2.9)	5,973 (6.9)	6,732 (7.8)
Cerebrovascular disease, n (%)	11,831 (6.2)	12,017 (6.3)	16,797 (19.4) ^b	18,367 (21.2) ^b
Congestive heart failure, n (%) ^a	11,586 (6.1)	12,704 (6.7)	17,908 (20.7)	19,574 (22.6)
Chronic pulmonary disease, n (%) ^a	47,778 (25.2)	50,301 (26.6)	28,441 (32.8)	29,908 (34.5)
Dementia, n (%) ^a	7,159 (3.8)	6,123 (3.2)	32,636 (37.7)	31,510 (36.4)
Diabetes with chronic complication, n (%)	15,732 (8.3) ^b	15,385 (8.1) ^b	14,400 (16.6)	14,230 (16.4)
Diabetes without chronic complication, n (%) ^a	39,407 (20.8)	37,749 (19.9)	24,360 (28.1)	23,844 (27.5)
Hemiplegia or paraplegia, n (%)	4,238 (2.2)	4,092 (2.2)	2,388 (2.8) ^b	2,613 (3.0) ^b
Mild liver disease, n (%) ^a	10,985 (5.8)	12,043 (6.4)	3,344 (3.9)	3,907 (4.5)
Metastatic solid tumor, n (%) ^a	927 (0.5)	1,373 (0.7)	924 (1.1)	1,350 (1.6)
Myocardial infarction, n (%) ^a	3,863 (2.0)	5,001 (2.6)	3,508 (4.0)	4,809 (5.6)
Moderate or severe liver disease, n (%)	1,247 (0.7) ^b	1,456 (0.8) ^b	561 (0.6)	625 (0.7)
Peptic ulcer disease, n (%) ^a	2,196 (1.2)	2,496 (1.3)	1,510 (1.7)	1,831 (2.1)
Peripheral vascular disease, n (%) ^a	17,239 (9.1)	15,030 (7.9)	29,476 (34.0)	26,247 (30.3)
Renal disease, n (%)	11,634 (6.1)	11,658 (6.2)	14,396 (16.6) ^b	15,687 (18.1) ^b
Rheumatic disease, n (%) ^a	3,449 (1.8)	4,145 (2.2)	2,337 (2.7)	2,867 (3.3)
Additional psychiatric medications, n (%)				
ADHD medication ^a	6,749 (3.6)	7,440 (3.9)	727 (0.8)	909 (1.0)

Anticholinergic ^a	48,581 (25.7)	42,937 (22.7)	14,148 (16.3)	11,202 (12.9)
Antidepressant ^a	117,873 (62.2)	121,616 (64.2)	53,288 (61.5)	53,720 (62.0)
Anxiety medication ^a	51,946 (27.4)	56,081 (29.6)	21,625 (25.0)	24,092 (27.8)
Mood stabilizer ^a	87,384 (46.1)	82,263 (43.4)	34,040 (39.3)	30,737 (35.5)
Sedative ^a	20,554 (10.9)	23,811 (12.6)	7,302 (8.4)	9,333 (10.8)

ADHD, attention-deficit hyperactivity disorder; AIDS, acquired immunodeficiency syndrome;

CCI, Charlson Comorbidity Index; HIV, human immunodeficiency virus; SD, standard deviation; TD, tardive dyskinesia.

^a $P < 0.05$ for dose reduction vs stable dose in both dose reduction cohorts.

^b $P < 0.05$ for dose reduction vs stable dose only in the indicated dose reduction cohort.

Table 3. Baseline Demographics of $\geq 30\%$ Dose Reduction Cohorts Stratified by Age

Characteristic	<65 Years		≥ 65 Years	
	Dose reduction (n=142,991)	Stable dose (n=142,991)	Dose reduction (n=68,584)	Stable dose (n=68,584)
Age, years, mean (SD) ^a	48.4 (10.6)	48.4 (10.6)	74.7 (7.8)	74.7 (7.8)
Schizophrenia duration, months, mean (SD) ^a	32.9 (21.2)	24.7 (21.7)	31.2 (21.3)	21.1 (21.0)
Sex, male, n (%)	79,831 (55.8)	79,831 (55.8)	23,986 (35.0)	23,986 (35.0)
Duration of follow-up, months, mean (SD) ^a	4.2 (6.5)	9.2 (8.8)	5.0 (6.8)	8.9 (8.4)
Index drug class, n (%)				
Typical antipsychotic	17,906 (12.5)	17,906 (12.5)	8,642 (12.6)	8,642 (12.6)
Atypical antipsychotic	125,085 (87.5)	125,085 (87.5)	59,942 (87.4)	59,942 (87.4)
Index year, n (%)				
2011	9,624 (6.7)	9,624 (6.7)	3,979 (5.8)	3,979 (5.8)
2012	21,935 (15.3)	21,935 (15.3)	10,194 (14.9)	10,194 (14.9)
2013	22,727 (15.9)	22,727 (15.9)	10,131 (14.8)	10,131 (14.8)
2014	22,783 (15.9)	22,783 (15.9)	10,143 (14.8)	10,143 (14.8)
2015	21,900 (15.3)	21,900 (15.3)	10,382 (15.1)	10,382 (15.1)
2016	22,009 (15.4)	22,009 (15.4)	11,165 (16.3)	11,165 (16.3)
2017	22,013 (15.4)	22,013 (15.4)	12,590 (18.4)	12,590 (18.4)
Comorbidity profile, n (%)				
Substance-related and addictive disorders ^a	47,927 (33.5)	53,507 (37.4)	8,862 (12.9)	10,834 (15.8)
Anxiety disorders ^a	39,662 (27.7)	43,471 (30.4)	20,372 (29.7)	22,989 (33.5)
Bipolar disorders ^a	48,850 (34.2)	51,375 (35.9)	17,223 (25.1)	17,621 (25.7)
Depressive disorders ^a	48,815 (34.1)	53,800 (37.6)	29,135 (42.5)	31,910 (46.5)
Personality disorders ^a	8,742 (6.1)	8,997 (6.3)	1,668 (2.4)	2,049 (3.0)
Schizophrenia-spectrum disorders (excluding	23,913 (16.7)	27,436 (19.2)	16,398 (23.9)	19,326 (28.2)

schizophrenia) ^a				
Sleep-wake disorders ^a	24,102 (16.9)	25,509 (17.8)	10,110 (14.7)	12,043 (17.6)
TD	1,036 (0.7) ^b	880 (0.6) ^b	1,058 (1.5)	1,049 (1.5)
Trauma- and stressor-related disorders ^a	12,974 (9.1)	14,218 (9.9)	2,956 (4.3)	3,644 (5.3)
Mean (SD) CCI score^a	1.0 (1.6)	1.0 (1.6)	2.3 (2.1)	2.4 (2.2)
AIDS/HIV, n (%) ^a	2,032 (1.4)	2,449 (1.7)	223 (0.3)	311 (0.5)
Cancer, n (%) ^a	3,870 (2.7)	4,184 (2.9)	4,731 (6.9)	5,368 (7.8)
Cerebrovascular disease, n (%) ^a	9,467 (6.6)	9,110 (6.4)	13,689 (20.0)	14,601 (21.3)
Congestive heart failure, n (%) ^a	9,320 (6.5)	9,646 (6.7)	14,604 (21.3)	15,514 (22.6)
Chronic pulmonary disease, n (%) ^a	37,160 (26.0)	38,134 (26.7)	22,700 (33.1)	23,637 (34.5)
Dementia, n (%) ^a	5,627 (3.9)	4,664 (3.3)	26,523 (38.7)	25,262 (36.8)
Diabetes with chronic complication, n (%) ^a	12,175 (8.5)	11,621 (8.1)	11,515 (16.8)	11,173 (16.3)
Diabetes without chronic complication, n (%) ^a	29,789 (20.8)	28,514 (19.9)	19,292 (28.1)	18,867 (27.5)
Hemiplegia or paraplegia, n (%) ^a	3,353 (2.3)	3,067 (2.1)	1,933 (2.8)	2,059 (3.0)
Mild liver disease, n (%) ^a	8,591 (6.0)	9,097 (6.4)	2,718 (4.0)	2,996 (4.4)
Metastatic solid tumor, n (%) ^a	724 (0.5)	1,018 (0.7)	756 (1.1)	1,063 (1.5)
Myocardial infarction, n (%) ^a	3,131 (2.2)	3,770 (2.6)	2,899 (4.2)	3,814 (5.6)
Moderate or severe liver disease, n (%)	1,020 (0.7) ^b	1,127 (0.8) ^b	470 (0.7)	484 (0.7)
Peptic ulcer disease, n (%) ^a	1,747 (1.2)	1,897 (1.3)	1,237 (1.8)	1,424 (2.1)
Peripheral vascular disease, n (%) ^a	13,374 (9.4)	11,374 (8.0)	23,587 (34.4)	20,800 (30.3)
Renal disease, n (%) ^a	9,113 (6.4)	8,828 (6.2)	11,605 (16.9)	12,457 (18.2)
Rheumatic disease, n (%) ^a	2,720 (1.9)	3,168 (2.2)	1,891 (2.8)	2,259 (3.3)
Additional psychiatric medications, n (%)				
ADHD medication ^a	5,263 (3.7)	5,580 (3.9)	573 (0.8)	724 (1.1)
Anticholinergic ^a	36,338 (25.4)	32,385 (22.6)	10,862 (15.8)	8,813 (12.8)
Antidepressant	90,307 (63.2) ^b	92,076 (64.4) ^b	42,470 (61.9)	42,534 (62.0)

Anxiety medication ^a	40,216 (28.1)	42,644 (29.8)	17,302 (25.2)	19,103 (27.9)
Mood stabilizer ^a	66,703 (46.6)	62,175 (43.5)	26,879 (39.2)	24,254 (35.4)
Sedative ^a	16,248 (11.4)	18,087 (12.6)	5,971 (8.7)	7,384 (10.8)

ADHD, attention-deficit hyperactivity disorder; AIDS, acquired immunodeficiency syndrome;

CCI, Charlson Comorbidity Index; HIV, human immunodeficiency virus; SD, standard deviation; TD, tardive dyskinesia.

^a $P < 0.05$ for dose reduction vs stable dose in both dose reduction cohorts.

^b $P < 0.05$ for dose reduction vs stable dose only in the indicated dose reduction cohort.

Table 4. Dose Distribution for Ten Most Frequently Used Antipsychotics During Stable Dose Period in the $\geq 10\%$ Dose Reduction Cohort Stratified by Age

Drug	<65 Years		≥ 65 Years	
	Dose reduction (n=189,386)	Stable dose (n=189,386)	Dose reduction (n=86,644)	Stable dose (n=86,644)
Risperidone, n (%)	39,259 (20.7)	38,267 (20.2)	24,048 (27.8)	22,537 (26.0)
Mean (SD) dose, mg	4.6 (2.5)	3.4 (2.2)	2.7 (2.1)	1.9 (1.8)
Quetiapine, n (%)	38,253 (20.2)	35,909 (19.0)	20,592 (23.8)	20,734 (23.9)
Mean (SD) dose, mg	476.8 (282.3)	331.0 (256.0)	259.6 (232.0)	168.2 (186.2)
Olanzapine, n (%)	31,817 (16.8)	29,119 (15.4)	17,459 (20.2)	16,709 (19.3)
Mean (SD) dose, mg	21.3 (9.7)	15.8 (8.7)	14.5 (8.9)	10.3 (7.3)
Aripiprazole, n (%)	17,144 (9.1)	27,159 (14.3)	6,271 (7.2)	8,878 (10.2)
Mean (SD) dose, mg	20.2 (10.2)	15.3 (10.0)	14.5 (9.9)	11.2 (9.5)
Clozapine, n (%)	18,554 (9.8)	9,163 (4.8)	3,136 (3.6)	1,454 (1.7)
Mean (SD) dose, mg	409.0 (181.9)	401.4 (185.1)	309.4 (173.7)	269.8 (183.5)
Ziprasidone, n (%)	11,803 (6.2)	10,649 (5.6)	2,603 (3.0)	2,699 (3.1)
Mean (SD) dose, mg	147.6 (60.9)	117.9 (56.0)	115.7 (56.9)	89.7 (53.5)
Haloperidol, n (%)	9,836 (5.2)	9,552 (5.0)	4,511 (5.2)	4,074 (4.7)
Mean (SD) dose, mg	15.9 (11.8)	11.4 (9.5)	8.9 (9.2)	6.3 (7.7)
Fluphenazine, n (%)	4,358 (2.3)	4,245 (2.2)	1,697 (2.0)	1,560 (1.8)
Mean (SD) dose, mg	18.8 (11.7)	13.5 (10.0)	13.7 (11.0)	9.7 (8.7)
Lurasidone, n (%)	4,833 (2.6)	8,741 (4.6)	745 (0.9)	1,402 (1.6)
Mean (SD) dose, mg	94.8 (39.4)	70.9 (38.0)	79.0 (38.3)	58.7 (34.9)

Paliperidone, n (%)	3,679 (1.9)	5,287 (2.8)	672 (0.8)	907 (1.0)
Mean (SD) dose, mg	9.2 (3.5)	7.4 (3.0)	7.6 (3.3)	6.1 (3.1)

SD, standard deviation.

Table 5. Dose Distribution for Ten Most Frequently Used Antipsychotics During Stable Dose Period in the $\geq 30\%$ Dose Reduction Cohort Stratified by Age

Drug	<65 Years		≥ 65 Years	
	Dose reduction (n=142,991)	Stable dose (n=142,991)	Dose reduction (n=68,584)	Stable dose (n=68,584)
Risperidone, n (%)	30,490 (21.3)	28,785 (20.1)	19,651 (28.7)	17,904 (26.1)
Mean (SD) dose, mg	4.4 (2.5)	3.4 (2.2)	2.6 (2.1)	1.9 (1.8)
Quetiapine, n (%)	29,773 (20.8)	28,785 (20.1)	16,574 (24.2)	16,515 (24.1)
Mean (SD) dose, mg	459.5 (281.8)	329.7 (255.7)	246.5 (226.2)	167.1 (185.6)
Olanzapine, n (%)	23,883 (16.7)	21,714 (15.2)	13,421 (19.6)	13,212 (19.3)
Mean (SD) dose, mg	21.4 (10.2)	15.7 (8.6)	13.8 (9.2)	10.3 (7.3)
Aripiprazole, n (%)	13,615 (9.5)	20,403 (14.3)	4,957 (7.2)	6,994 (10.2)
Mean (SD) dose, mg	20.0 (10.7)	15.2 (9.9)	14.1 (10.2)	11.1 (9.1)
Clozapine, n (%)	10,690 (7.5)	6,849 (4.8)	1,998 (2.9)	1,153 (1.7)
Mean (SD) dose, mg	393.1 (185.0)	402.0 (183.9)	296.1 (172.7)	268.1 (180.0)
Ziprasidone, n (%)	8,903 (6.2)	8,051 (5.6)	2,027 (3.0)	2,082 (3.0)
Mean (SD) dose, mg	144.7 (63.3)	118.0 (55.7)	110.3 (57.7)	88.5 (53.7)
Haloperidol, n (%)	7,724 (5.4)	7,484 (5.2)	3,615 (5.3)	3,215 (4.7)
Mean (SD) dose, mg	15.5 (11.7)	11.5 (9.6)	8.6 (8.9)	6.3 (7.7)
Fluphenazine, n (%)	3,573 (2.5)	3,302 (2.3)	1,367 (2.0)	1,224 (1.8)
Mean (SD) dose, mg	18.2 (11.3)	13.4 (10.0)	13.2 (10.2)	9.7 (8.6)
Lurasidone, n (%)	3,872 (2.7)	6,577 (4.6)	613 (0.9)	1,080 (1.6)
Mean (SD) dose, mg	91.8 (39.2)	71.0 (38.1)	75.2 (37.5)	58.3 (34.8)

Paliperidone, n (%)	3,074 (2.1)	3,951 (2.8)	575 (0.8)	708 (1.0)
Mean (SD) dose, mg	8.8 (3.6)	7.4 (3.0)	7.3 (3.2)	6.0 (3.0)

SD, standard deviation.

Table 6. Multivariable Cox Regression Analyses of the Effects of $\geq 10\%$ Antipsychotic Dose Reductions Stratified by Age^a

Outcome	<65 Years			≥ 65 Years		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
All-cause ER visit	1.12	(1.11–1.14)	<0.001	0.96	(0.95–0.98)	<0.001
All-cause inpatient visit	1.35	(1.33–1.37)	<0.001	1.01	(0.99–1.03)	0.159
Schizophrenia relapse	1.30	(1.28–1.32)	<0.001	1.09	(1.06–1.12)	<0.001
Other psychiatric relapse (excluding schizophrenia)	1.19	(1.17–1.20)	<0.001	1.00	(0.98–1.02)	0.800
TD diagnosis ^b	1.53	(1.37–1.71)	<0.001	1.31	(1.17–1.47)	<0.001

ADHD, attention-deficit hyperactivity disorder; CCI, Charlson Comorbidity Index; CI, confidence interval; ER, emergency room; HR, hazard ratio; TD, tardive dyskinesia.

^aCovariates included age; disease duration; CCI; substance-related and addictive, anxiety, bipolar and related, depressive, personality, schizophrenia spectrum (excluding schizophrenia), sleep-wake, trauma-related, and stressor-related disorders; TD; psychotherapy; antidepressants; anticholinergics; sedatives; mood stabilizers; anxiety medications; and ADHD medications.

^bPatients with TD during the 6-month period prior to the index date were excluded from the TD analyses. For the dose reduction cohort, the index date was defined as the date of the initial dose reduction. For the stable dose cohort, the index date was defined as the date of the first prescription fill after the first stable dose monotherapy period of ≥ 90 days.

Table 7. Multivariable Cox Regression Analyses of the Effects of $\geq 30\%$ Antipsychotic Dose Reductions Stratified by Age^a

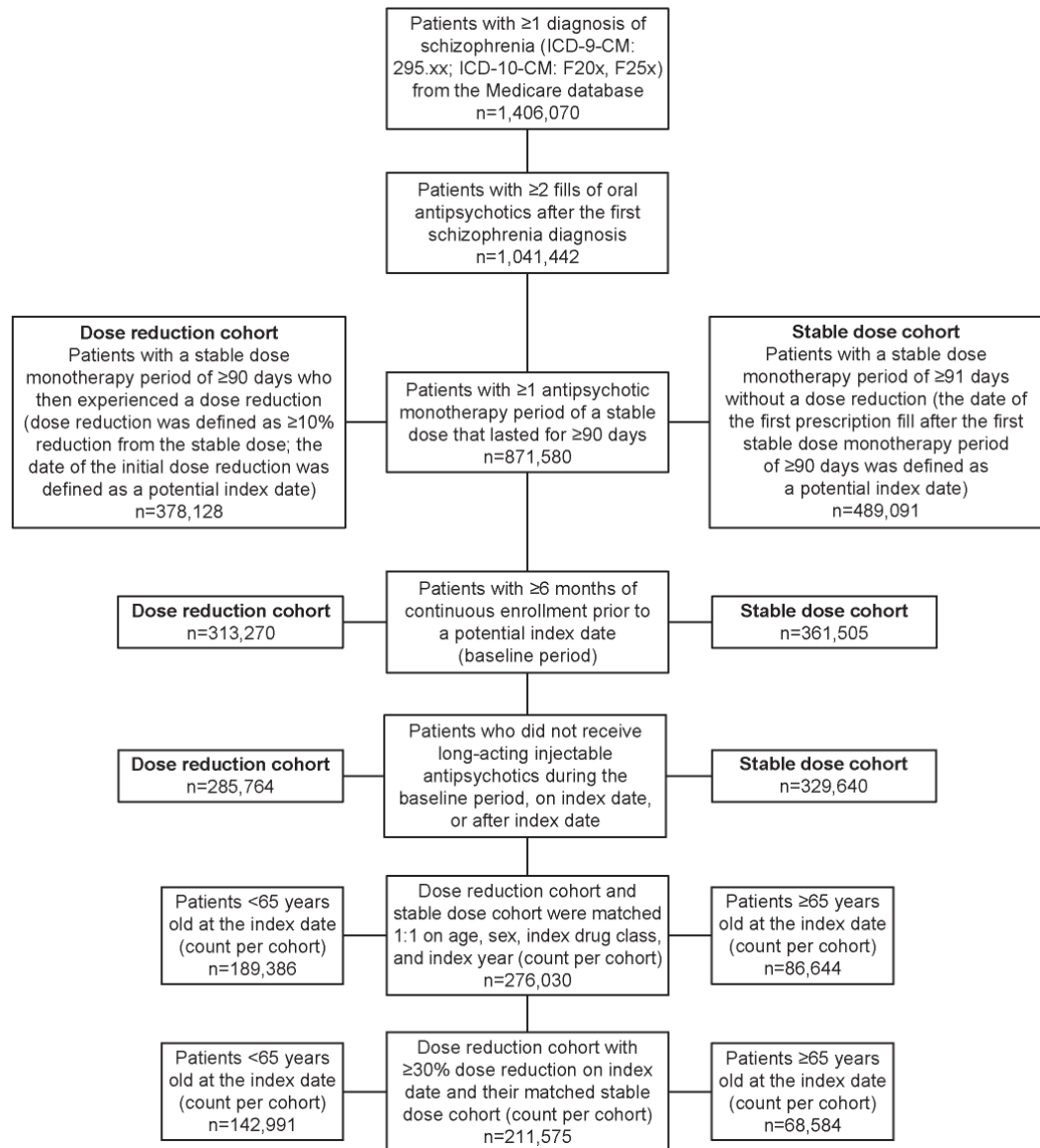
Outcome	<65 Years			≥ 65 Years		
	HR	95% CI	P value	HR	95% CI	P value
All-cause ER visit	1.16	(1.14–1.18)	<0.001	0.99	(0.97–1.01)	0.211
All-cause inpatient visit	1.40	(1.38–1.43)	<0.001	1.04	(1.02–1.06)	<0.001
Schizophrenia relapse	1.32	(1.29–1.35)	<0.001	1.08	(1.05–1.11)	<0.001
Other psychiatric relapse (excluding schizophrenia)	1.23	(1.21–1.25)	<0.001	1.02	(1.00–1.05)	0.071
TD diagnosis ^b	1.47	(1.29–1.68)	<0.001	1.29	(1.13–1.46)	<0.001

ADHD, attention-deficit hyperactivity disorder; CCI, Charlson Comorbidity Index; CI, confidence interval; ER, emergency room; HR, hazard ratio; TD, tardive dyskinesia.

^aCovariates included age; disease duration; CCI; substance-related and addictive, anxiety, bipolar and related, depressive, personality, schizophrenia spectrum (excluding schizophrenia), sleep-wake, trauma-related, and stressor-related disorders; TD; psychotherapy; antidepressants; anticholinergics; sedatives; mood stabilizers; anxiety medications; and ADHD medications.

^bPatients with TD during the 6-month period prior to the index date were excluded from the TD analyses. For the dose reduction cohort, the index date was defined as the date of the initial dose reduction. For the stable dose cohort, the index date was defined as the date of the first prescription fill after the first stable dose monotherapy period of ≥ 90 days.

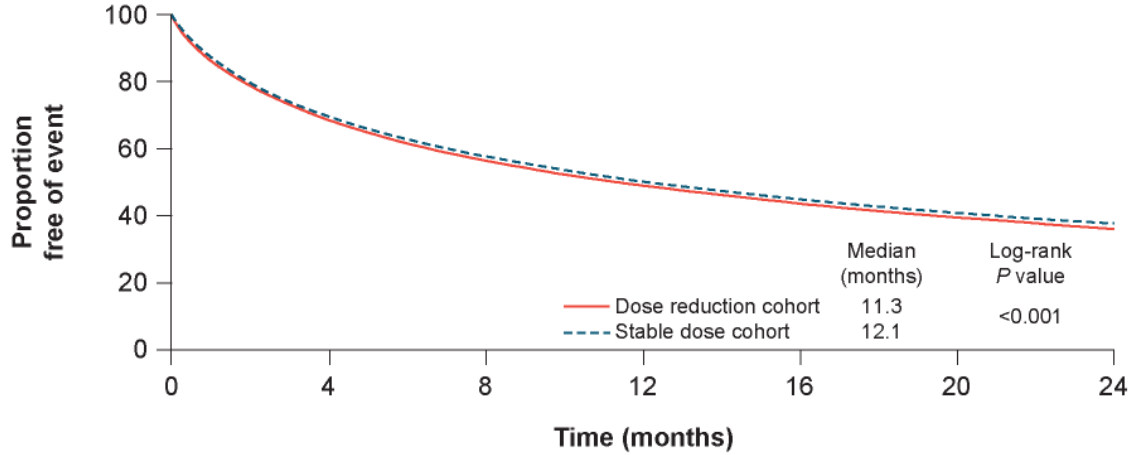
Fig. 1 Patient Selection Flow Diagram



ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*;
 ICD-10-CM, *International Classification of Diseases, Tenth Revision, Clinical Modification*.

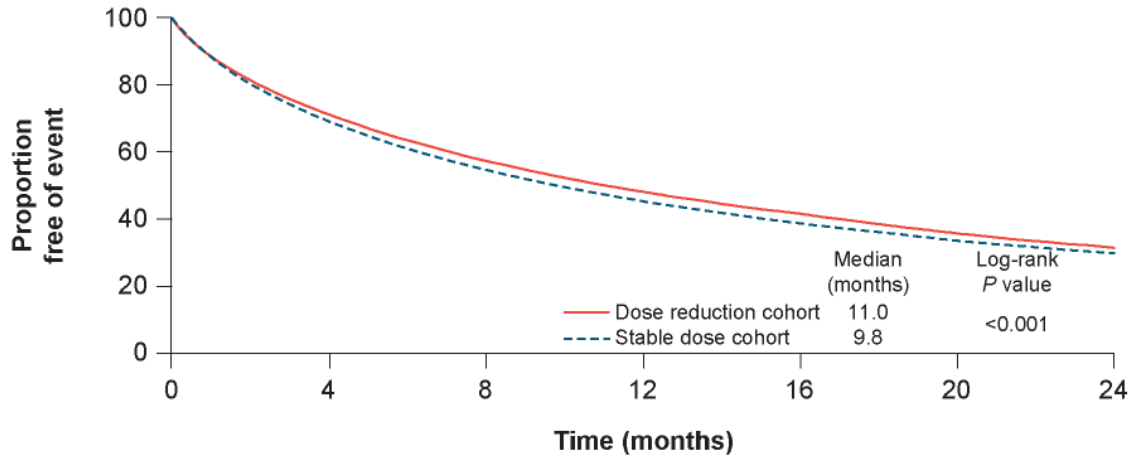
Fig. 2 Time to All-Cause ER Visit With $\geq 10\%$ and $\geq 30\%$ Dose Reductions Stratified by Age

A. $\geq 10\%$ Dose Reduction (<65 Years)



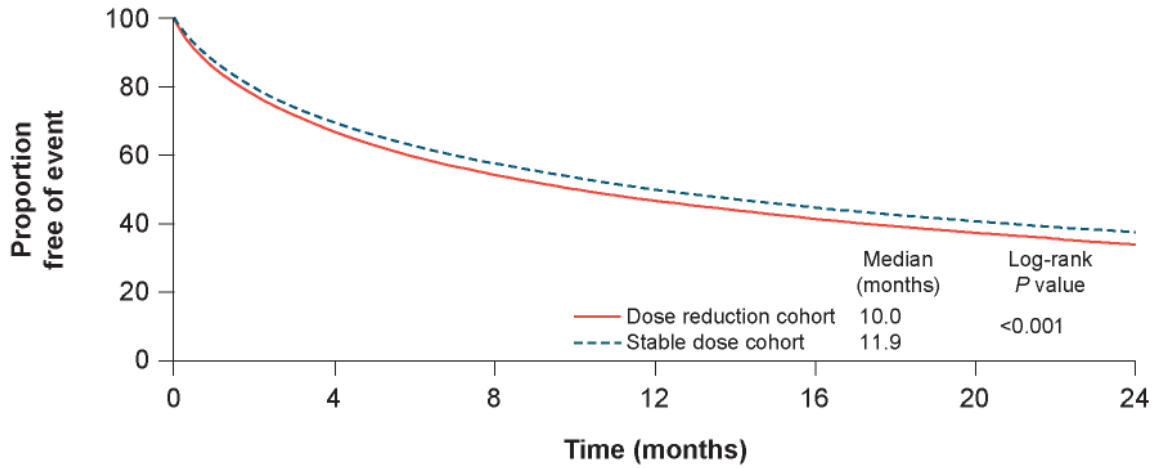
n at risk		0	4	8	12	16	20	24
Dose reduction cohort	189,386	44,071	25,306	16,683	11,849	8,700	6,481	
Stable dose cohort	189,386	81,474	51,870	37,154	28,161	22,005	17,532	

B. $\geq 10\%$ Dose Reduction (≥ 65 Years)



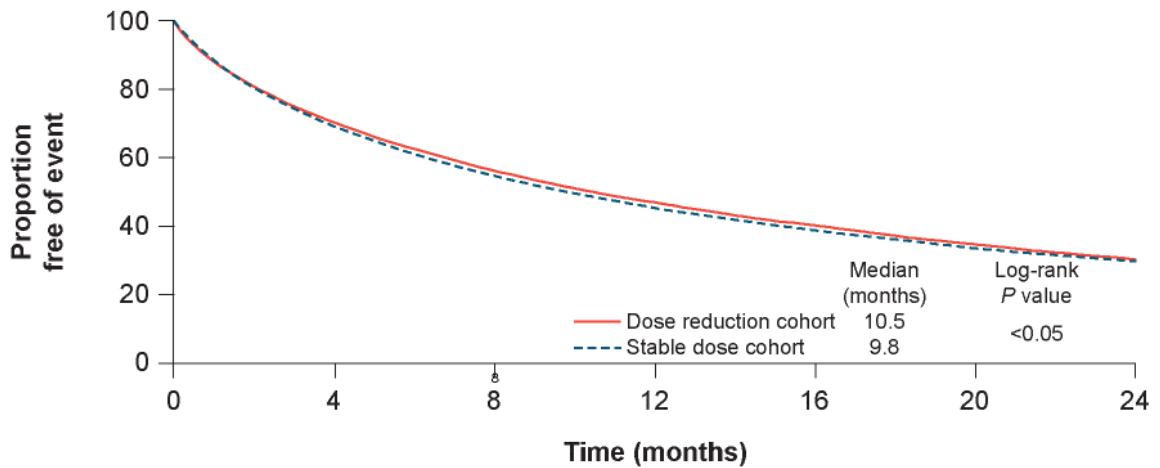
n at risk		0	4	8	12	16	20	24
Dose reduction cohort	86,644	24,532	13,508	8,356	5,488	3,642	2,509	
Stable dose cohort	86,644	38,421	22,985	15,247	10,802	7,801	5,841	

C. $\geq 30\%$ Dose Reduction (<65 Years)



	n at risk						
Dose reduction cohort	142,991	28,578	15,856	10,234	7,147	5,194	3,846
Stable dose cohort	142,991	61,334	38,900	27,801	21,029	16,444	13,092

D. $\geq 30\%$ Dose Reduction (≥ 65 Years)



	n at risk						
Dose reduction cohort	68,584	18,117	9,779	5,985	3,863	2,561	1,736
Stable dose cohort	68,584	30,401	18,148	12,015	8,502	6,147	4,601

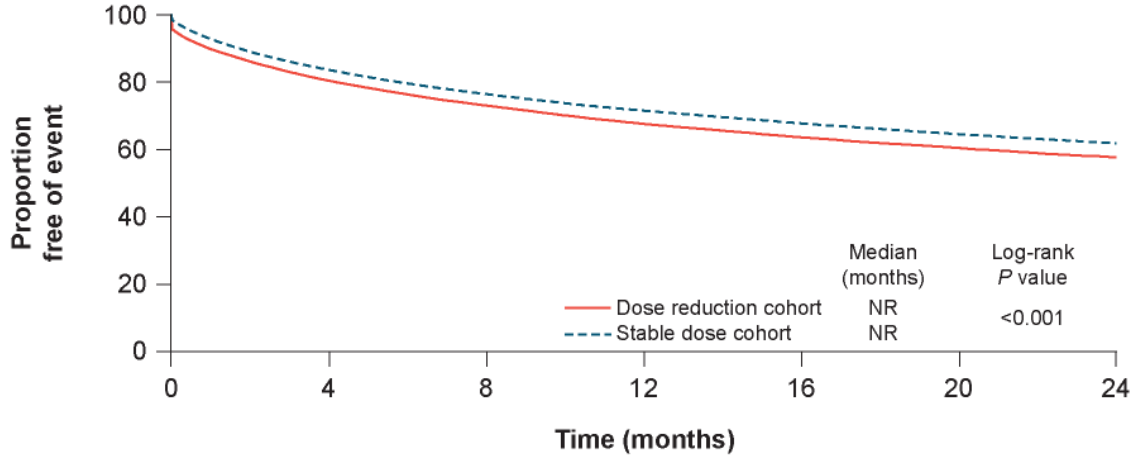
ER, emergency room.

Descriptive caption: These are Kaplan-Meier graphs describing the time to all-cause ER visit for the $\geq 10\%$ and $\geq 30\%$ dose reduction and stable dose cohorts stratified by age (<65 years vs ≥ 65 years). The x-axis represents time in months at an interval of 4 months, and the y-axis represents proportion of patients free of event. Patients aged <65 years had a median time to all-cause ER

visit of 11.3 months in the $\geq 10\%$ dose reduction cohort and 12.1 months in the stable dose cohort ($P < 0.001$). Patients aged ≥ 65 years had a median time to all-cause ER visit of 11.0 months in the $\geq 10\%$ dose reduction cohort and 9.8 months for the stable dose cohort ($P < 0.001$). Patients aged < 65 years had a median time to all-cause ER visit of 10.0 months in the $\geq 30\%$ dose reduction cohort and 11.9 months in the stable dose cohort for ($P < 0.001$). Patients aged ≥ 65 years had a median time to all-cause ER visit of 10.5 months in the $\geq 30\%$ dose reduction cohort and 9.8 months in the stable dose cohort ($P < 0.05$).

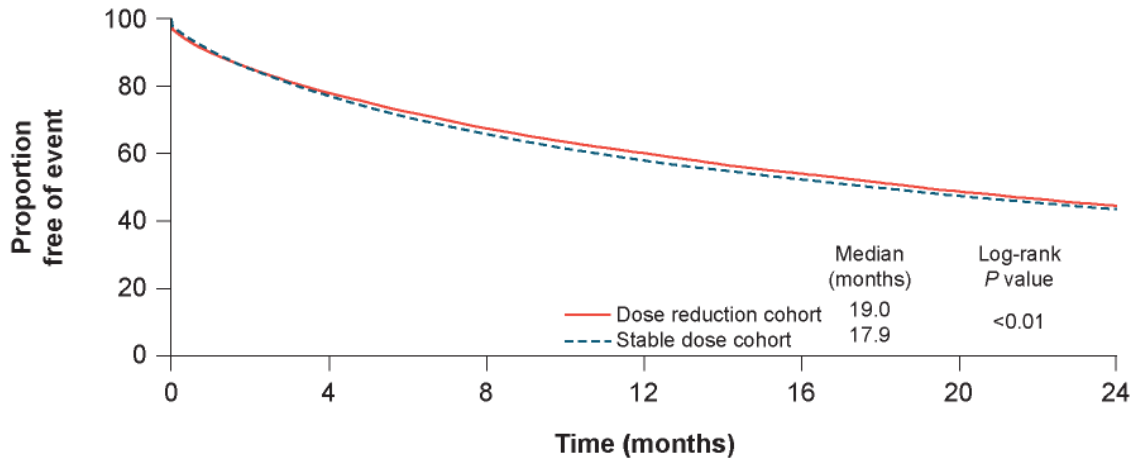
Fig. 3 Time to All-Cause Inpatient Visit With $\geq 10\%$ and $\geq 30\%$ Dose Reductions Stratified by Age

A. $\geq 10\%$ Dose Reduction (<65 Years)



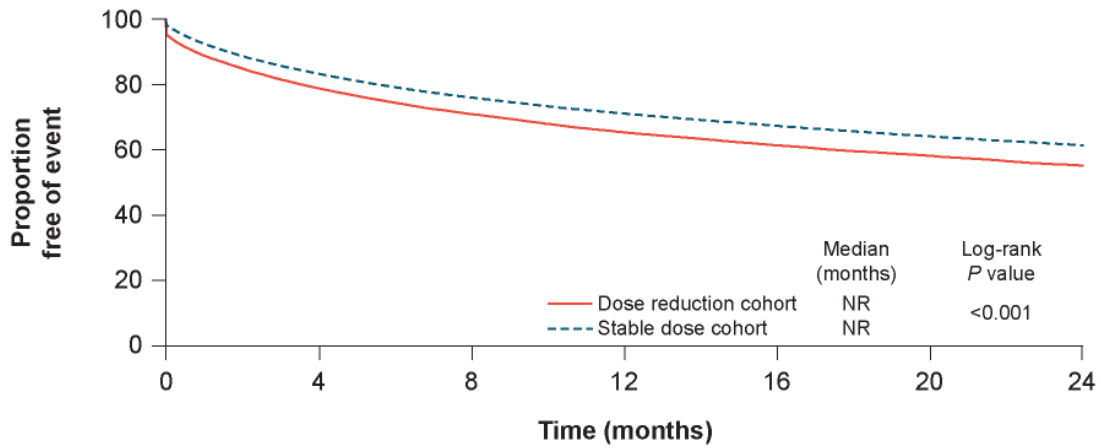
n at risk		0	4	8	12	16	20	24
Dose reduction cohort	189,386	51,219	31,880	22,034	16,295	12,383	9,512	
Stable dose cohort	189,386	96,815	66,500	50,349	39,760	32,086	26,159	

B. $\geq 10\%$ Dose Reduction (≥ 65 Years)



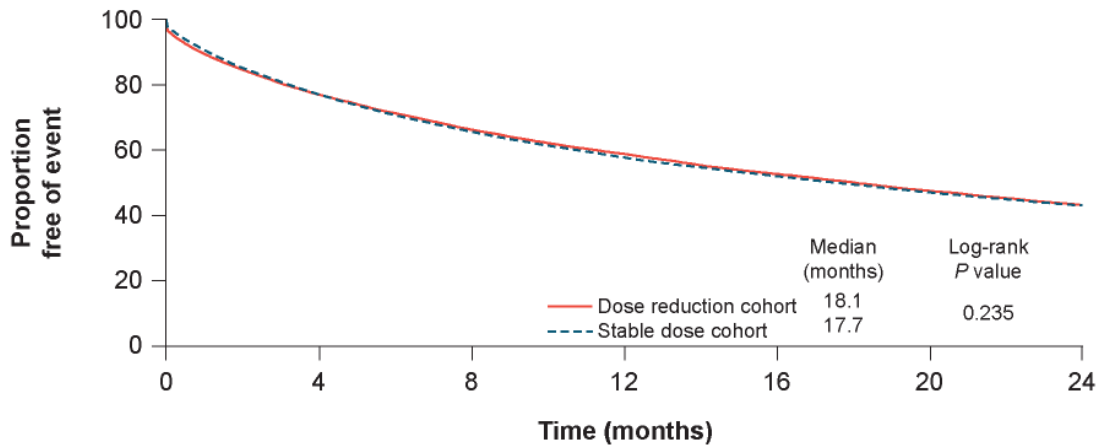
n at risk		0	4	8	12	16	20	24
Dose reduction cohort	86,644	26,783	15,691	10,220	7,000	4,890	3,475	
Stable dose cohort	86,644	42,994	27,543	19,219	14,240	10,691	8,183	

C. $\geq 30\%$ Dose Reduction (<65 Years)



	n at risk						
Dose reduction cohort	142,991	33,487	20,204	13,668	9,970	7,498	5,708
Stable dose cohort	142,991	72,929	49,892	37,744	29,713	23,933	19,485

D. $\geq 30\%$ Dose Reduction (≥ 65 Years)



	n at risk						
Dose reduction cohort	68,584	19,767	11,412	7,371	4,993	3,479	2,438
Stable dose cohort	68,584	34,043	21,723	15,136	11,169	8,369	6,408

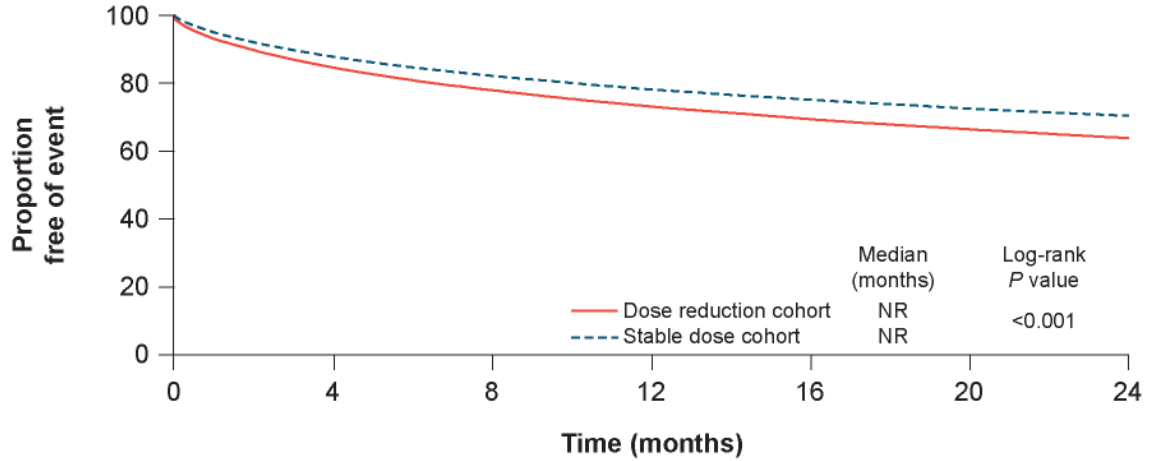
NR, not reached.

Descriptive caption: These are Kaplan-Meier graphs describing the time to all-cause inpatient visit for the $\geq 10\%$ and $\geq 30\%$ dose reduction and stable dose cohorts stratified by age (<65 years vs ≥ 65 years). The x-axis represents time in months at an interval of 4 months, and the y-axis represents proportion of patients free of event. Patients aged <65 years did not reach the median time to all-cause inpatient visit in the $\geq 10\%$ and $\geq 30\%$ dose reduction and stable dose cohorts

($P < 0.001$ for both comparisons). Patients aged ≥ 65 years had a median time to all-cause inpatient visit of 19.0 months in the $\geq 10\%$ dose reduction cohort and 17.9 months in the stable dose cohort ($P < 0.01$). Patients aged ≥ 65 years had a median time to all-cause inpatient visit of 18.1 months in the $\geq 30\%$ dose reduction cohort and 17.7 months in the stable dose cohort ($P = 0.235$).

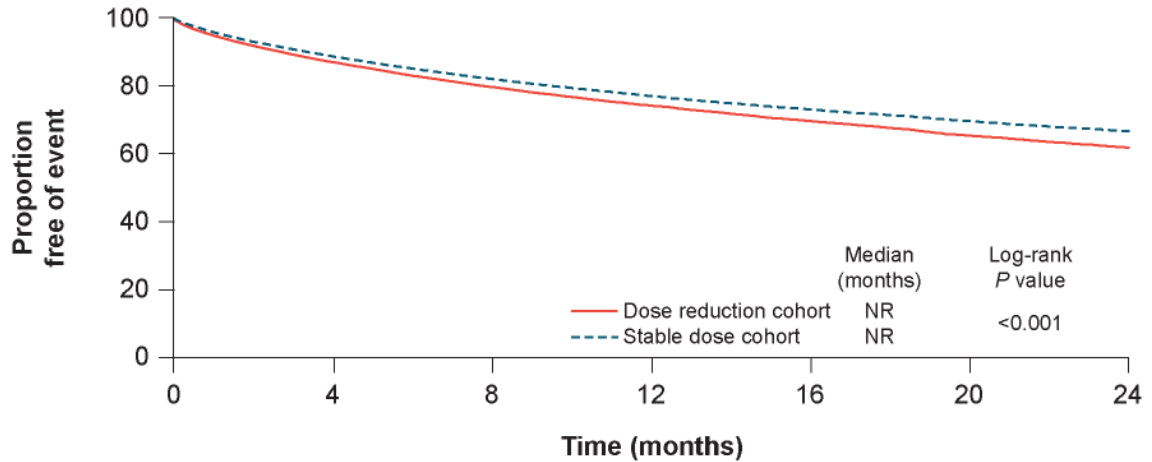
Fig. 4 Time to Schizophrenia Relapse^a With $\geq 10\%$ and $\geq 30\%$ Dose Reductions Stratified by Age

A. $\geq 10\%$ Dose Reduction (<65 Years)



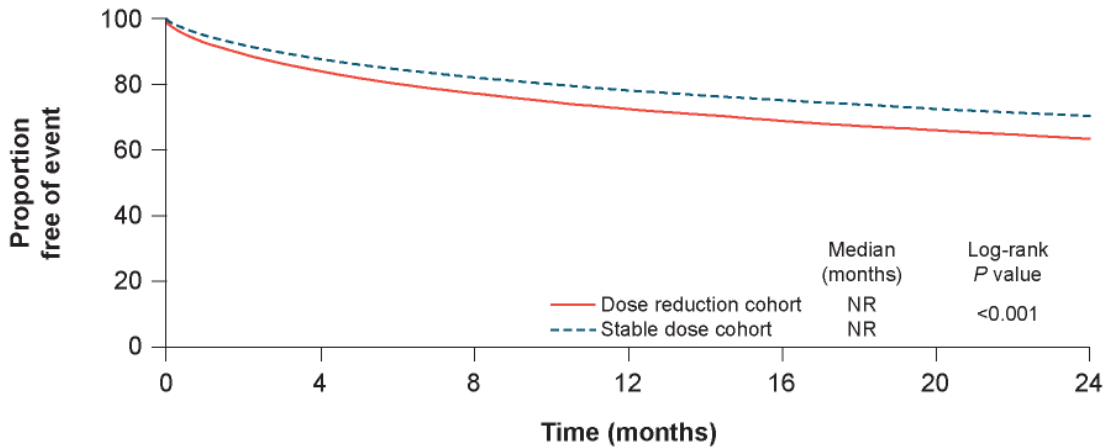
	n at risk						
Dose reduction cohort	189,386	52,888	32,888	22,821	16,923	12,831	9,852
Stable dose cohort	189,386	99,961	69,404	52,870	41,954	34,051	27,955

B. $\geq 10\%$ Dose Reduction (≥ 65 Years)



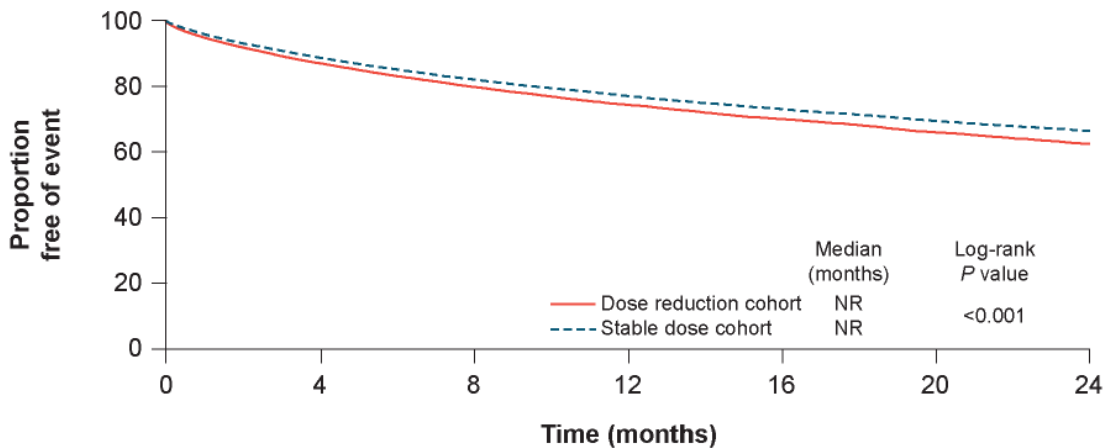
	n at risk						
Dose reduction cohort	86,644	28,724	17,242	11,384	7,965	5,638	4,074
Stable dose cohort	86,644	46,729	31,090	22,340	16,903	12,943	10,062

C. $\geq 30\%$ Dose Reduction (<65 Years)



n at risk		0	4	8	12	16	20	24
Dose reduction cohort	142,991	34,916	21,135	14,393	10,540	7,927	6,059	
Stable dose cohort	142,991	75,350	52,191	39,749	31,487	25,469	20,883	

D. $\geq 30\%$ Dose Reduction (≥ 65 Years)



n at risk		0	4	8	12	16	20	24
Dose reduction cohort	68,584	21,402	12,697	8,324	5,796	4,108	2,934	
Stable dose cohort	68,584	36,953	24,529	17,602	13,261	10,132	7,890	

ER, emergency room; NR, not reached.

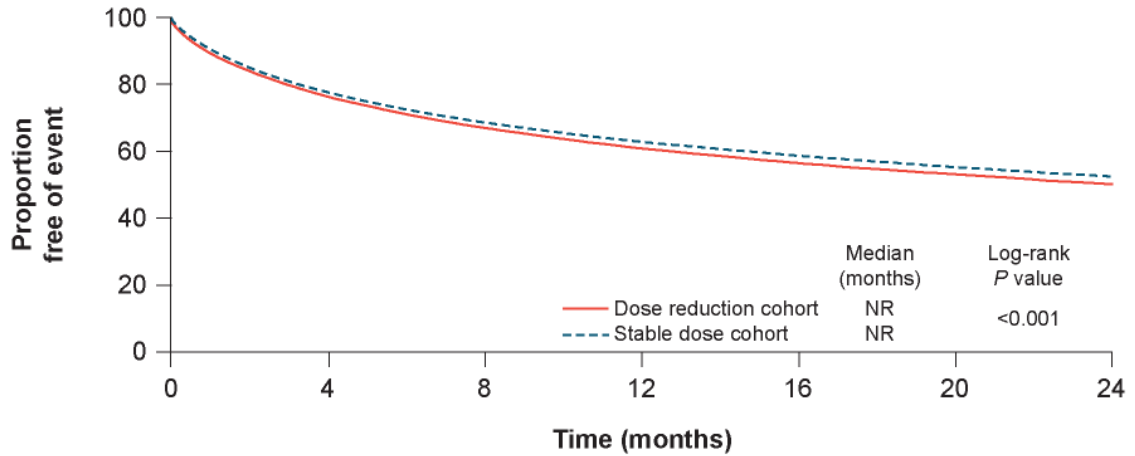
^aSchizophrenia relapse was defined as an inpatient admission or ER visit for schizophrenia.

Descriptive caption: These are Kaplan-Meier graphs describing the time to schizophrenia relapse for the $\geq 10\%$ and $\geq 30\%$ dose reduction and stable dose cohorts stratified by age (<65 years vs ≥ 65 years). The x-axis represents time in months at an interval of 4 months, and the y-axis represents proportion of patients free of event. Patients aged <65 years and ≥ 65 years did not

reach the median time to schizophrenia relapse in both the $\geq 10\%$ and $\geq 30\%$ dose reduction and stable dose cohorts ($P < 0.001$ for all).

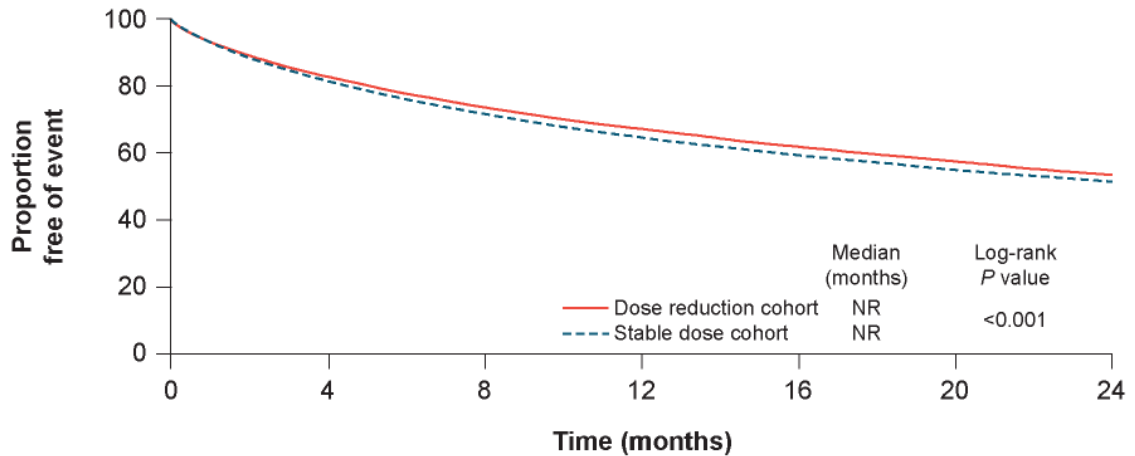
Fig. 5 Time to Other Psychiatric Relapse (Excluding Schizophrenia)^a With $\geq 10\%$ and $\geq 30\%$ Dose Reductions Stratified by Age

A. $\geq 10\%$ Dose Reduction (<65 Years)



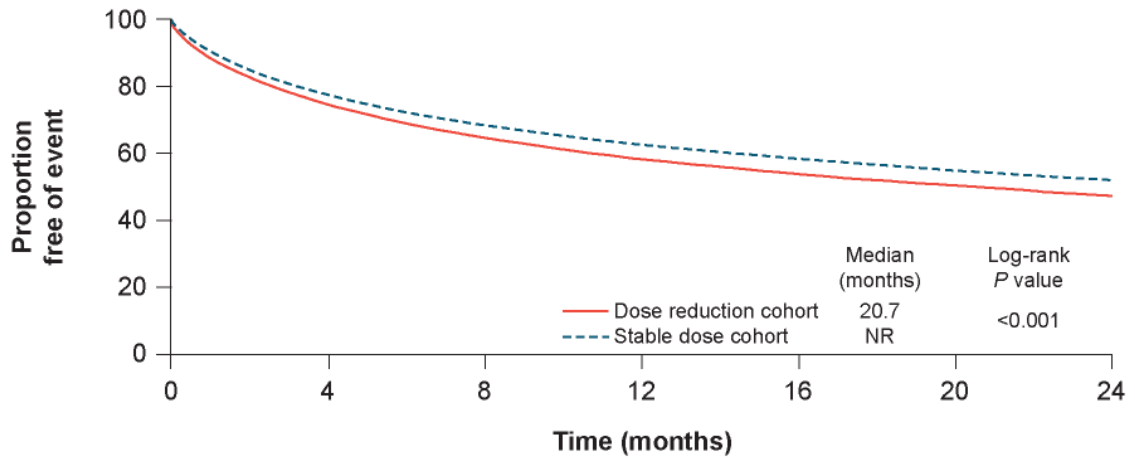
	n at risk						
Dose reduction cohort	189,386	48,776	29,571	20,254	14,899	11,263	8,644
Stable dose cohort	189,386	90,596	60,875	45,577	35,746	28,728	23,357

B. $\geq 10\%$ Dose Reduction (≥ 65 Years)



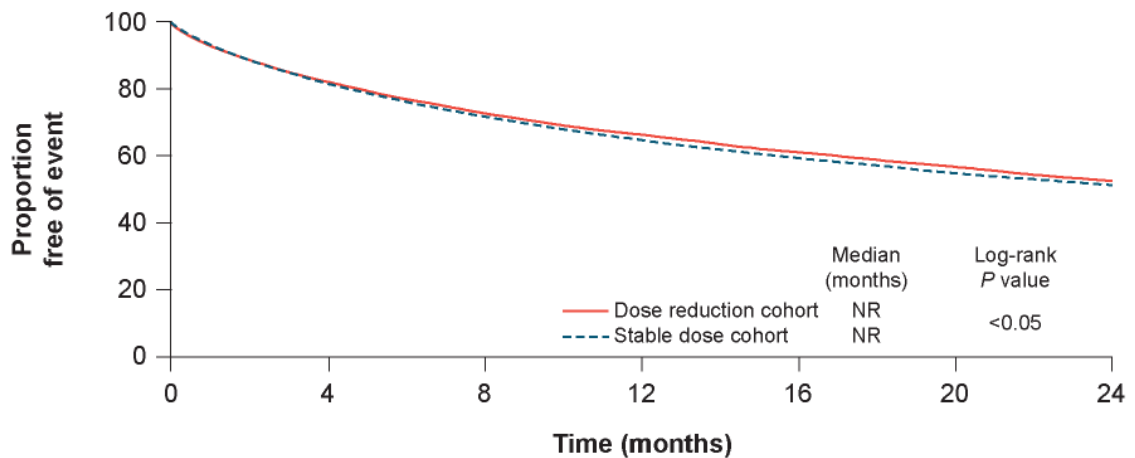
	n at risk						
Dose reduction cohort	86,644	27,686	16,414	10,719	7,403	5,230	3,737
Stable dose cohort	86,644	43,913	28,326	19,883	14,767	11,146	8,603

C. $\geq 30\%$ Dose Reduction (<65 Years)



	n at risk						
Dose reduction cohort	142,991	31,758	18,627	12,467	9,028	6,751	5,139
Stable dose cohort	142,991	68,274	45,731	34,212	26,751	21,433	17,391

D. $\geq 30\%$ Dose Reduction (≥ 65 Years)



	n at risk						
Dose reduction cohort	68,584	20,480	11,952	7,751	5,313	3,735	2,630
Stable dose cohort	68,584	34,796	22,373	15,693	11,594	8,731	6,737

ER, emergency room; NR, not reached.

^aPsychiatric relapse was defined as an inpatient admission or ER visit for psychiatric conditions, excluding schizophrenia and schizoaffective disorder.

Descriptive caption: These are Kaplan-Meier graphs describing the time to other psychiatric relapse, excluding schizophrenia, for the $\geq 10\%$ and $\geq 30\%$ dose reduction and stable dose cohorts

stratified by age (<65 years vs ≥ 65 years). The x-axis represents time in months at an interval of 4 months, and the y-axis represents proportion of patients free of event. Patients aged <65 years and ≥ 65 years did not reach the median time to other psychiatric relapse in the $\geq 10\%$ dose reduction and stable dose cohorts ($P < 0.001$ for both comparisons). Patients aged <65 years had a median time to other psychiatric relapse of 20.7 months in the $\geq 30\%$ dose reduction cohort and did not reach the median time in the stable dose cohort ($P < 0.001$). Patients aged ≥ 65 years did not reach the median time to other psychiatric relapse in the $\geq 30\%$ dose reduction and stable dose cohorts ($P < 0.05$).