

# Appendix for: *Buprenorphine & methadone dosing strategies to reduce risk of relapse in the treatment of opioid use disorder*

## A1 Inclusion/Exclusion criteria

We use data harmonized across three large randomized trials for OUD treatment that were part of the NIDA Clinical Trials Network (CTN): CTN0027,<sup>1,2</sup> which randomized 1,269 participants to either BUP-NX or methadone, conducted 2006-2010; Phase 2 of CTN0030,<sup>3</sup> which randomized 360 participants to BUP-NX and standard medical management vs. BUP-NX and individual drug counseling, conducted 2006-2009; and CTN0051,<sup>4</sup> which randomized 570 participants to either extended release naltrexone or BUP-NX, conducted 2014-2017 (we exclude the extended release naltrexone arm of this trial). All included patient treatment and monitoring over 12 weeks.

All three trials enrolled adult participants over age 18 who met DSM-IV-TR criteria for opioid dependence or DSM-5 diagnosis of OUD. Consistent with the goals of the CTN,<sup>5</sup> the trials were broadly inclusive to treatment-seeking OUD patients and were conducted in community-based treatment programs across the US. Individuals were excluded if they had major medical and unstable psychiatric co-morbidities or were pregnant or planning to get pregnant. CTN0027 and CTN0051 included patients currently using all types of opioids, predominantly heroin users, while CTN0030 was restricted to those currently using prescription opioids and not currently using heroin. CTN0027 included patients who presented for treatment at methadone clinics, CTN0030 included patients who presented for office-based treatment, and CTN0051 included patients who presented for short-term inpatient treatment.

## A2 Analytic Details

- $d(L_{t-1}) = 1$  denotes increased dose at week  $t$  in response to the values  $L_{t-1}$ . Let  $d1$  denote the first treatment strategy of increasing dose in response to use:  $d1(L_{t-1}) = 1$  if there was sub-threshold illicit opioid use and if dose was below the observed maximum ( $< 32\text{mg}$  for BUP-NX,  $< 397\text{mg}$  for methadone) and at time  $t - 1$ , and  $d1(L_{t-1}) = 0$  otherwise.
- Let  $d2$  denote the second strategy of increasing dose until a minimum threshold is reached:  $d2(L_{t-1}) = 1$  if BUP-NX dose was  $< 16\text{mg}$  or methadone dose was  $< 100\text{mg}$  at time  $t - 1$ , and  $d2(L_{t-1}) = 0$  otherwise.
- Let  $d3$  denote the hybrid strategy:  $d3(L_{t-1}) = 1$  if i) BUP-NX dose was  $< 16\text{mg}$  or methadone dose was  $< 100\text{mg}$  or if ii) there was sub-threshold illicit opioid use and if dose was below the observed maximum at time  $t - 1$ , and  $d3(L_{t-1}) = 0$  otherwise.
- Let  $d4$  denote the strategy of holding dose constant:  $d4(L_{t-1}) = 0$ .

Figure A1: Directed acyclic graph depicting the longitudinal data. Nodes at timepoints  $t \in \{4-10\}$  are omitted for readability. L2 includes baseline covariates and time-varying covariates at week 1;  $L_t$  for  $t \in \{3-11\}$  includes time-varying covariates of use and dose at time  $t-1$  and relapse at time  $t$ ;  $A_t$  for  $t \in \{2-11\}$  denotes whether or not a dose increase happened at time  $t$ . All nodes are affected by all previous nodes. Pink lines denote relationships that contribute to the longitudinal effect estimate.

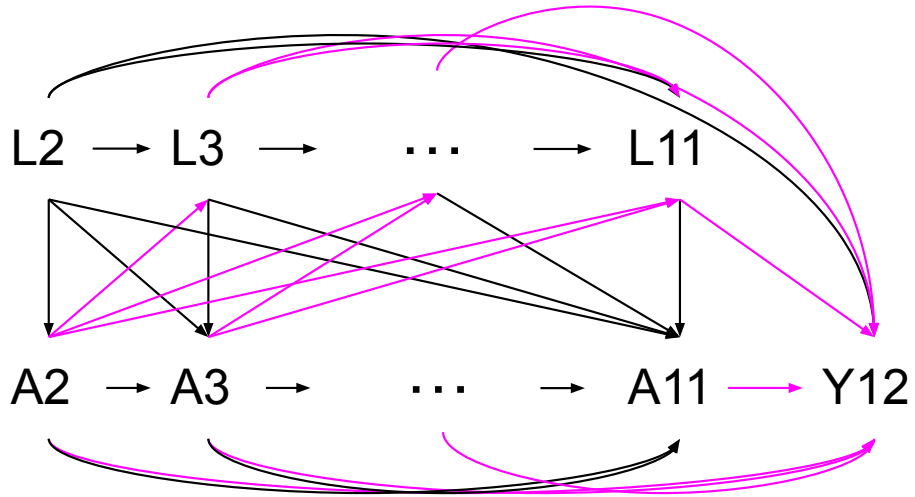


Table A1: Effect estimates on the additive scale (risk differences, RD) and multiplicative scale (risk ratios, RR) and their 95% confidence intervals (CIs) comparing dosing strategies {d1, d2, d3} to the constant dose strategy d4 on risk of relapse across weeks 3-12 of treatment. Effect estimates given separately for BUP-NX treatment and for methadone treatment.

Wk.	BUP-NX				Methadone				
	RD		RR		RD		RR		
	$\hat{\psi}$	95% CI	$\hat{\psi}$	95% CI	$\hat{\psi}$	95% CI	$\hat{\psi}$	95% CI	
<b>d1 vs. d4</b>									
3	0.00	-0.02, 0.02	1.03	0.71, 1.36	0.01	-0.03, 0.06	1.13	0.74, 1.52	
4	-0.13	-0.16, -0.10	0.49	0.26, 0.72	-0.16	-0.21, -0.11	0.47	0.24, 0.69	
5	-0.11	-0.14, -0.07	0.63	0.46, 0.80	-0.12	-0.18, -0.06	0.58	0.33, 0.83	
6	-0.04	-0.08, -0.00	0.90	0.79, 1.00	-0.08	-0.14, -0.02	0.84	0.71, 0.96	
7	-0.07	-0.11, -0.03	0.84	0.74, 0.95	-0.09	-0.14, -0.04	0.82	0.71, 0.93	
8	-0.04	-0.08, 0.00	0.91	0.81, 1.01	-0.10	-0.16, -0.04	0.82	0.71, 0.93	
9	-0.03	-0.08, 0.03	0.94	0.82, 1.07	-0.14	-0.19, -0.09	0.77	0.67, 0.87	
10	-0.05	-0.10, 0.00	0.90	0.79, 1.01	-0.10	-0.16, -0.05	0.83	0.73, 0.93	
11	-0.04	-0.09, 0.02	0.93	0.82, 1.04	-0.10	-0.16, -0.04	0.84	0.73, 0.95	
12	-0.04	-0.09, 0.01	0.93	0.82, 1.03	-0.10	-0.15, -0.05	0.84	0.74, 0.93	
<b>d2 vs. d4</b>									
3	0.00	-0.01, 0.01	1.01	0.84, 1.17	0.00	-0.04, 0.05	1.04	0.61, 1.48	
4	-0.07	-0.09, -0.06	0.71	0.64, 0.79	-0.17	-0.22, -0.12	0.42	0.13, 0.71	
5	-0.06	-0.08, -0.04	0.79	0.72, 0.86	-0.14	-0.20, -0.07	0.52	0.22, 0.82	
6	-0.04	-0.06, -0.02	0.89	0.85, 0.94	-0.09	-0.15, -0.03	0.82	0.68, 0.96	
7	-0.05	-0.07, -0.03	0.89	0.84, 0.93	-0.10	-0.17, -0.04	0.80	0.67, 0.93	
8	-0.04	-0.06, -0.01	0.92	0.87, 0.97	-0.10	-0.16, -0.04	0.82	0.70, 0.95	
9	-0.03	-0.06, -0.01	0.93	0.88, 0.98	-0.14	-0.21, -0.08	0.76	0.64, 0.88	
10	-0.04	-0.06, -0.02	0.92	0.88, 0.96	-0.10	-0.17, -0.04	0.82	0.71, 0.94	
11	-0.03	-0.05, -0.01	0.94	0.89, 0.98	-0.11	-0.17, -0.04	0.82	0.71, 0.94	
12	-0.03	-0.05, -0.01	0.94	0.90, 0.98	-0.11	-0.18, -0.05	0.82	0.70, 0.93	
<b>d3 vs. d4</b>									
3	0.00	-0.02, 0.02	1.03	0.72, 1.34	0.01	-0.03, 0.06	1.13	0.71, 1.55	
4	-0.14	-0.16, -0.11	0.46	0.29, 0.62	-0.16	-0.22, -0.11	0.45	0.17, 0.73	
5	-0.12	-0.15, -0.09	0.59	0.46, 0.72	-0.12	-0.18, -0.06	0.57	0.29, 0.84	
6	-0.07	-0.09, -0.04	0.83	0.76, 0.90	-0.08	-0.14, -0.01	0.84	0.71, 0.98	
7	-0.10	-0.12, -0.07	0.77	0.71, 0.84	-0.09	-0.15, -0.03	0.83	0.71, 0.94	
8	-0.08	-0.11, -0.05	0.82	0.75, 0.90	-0.09	-0.15, -0.04	0.83	0.72, 0.94	
9	-0.07	-0.10, -0.03	0.86	0.78, 0.94	-0.13	-0.19, -0.07	0.78	0.68, 0.89	
10	-0.07	-0.11, -0.04	0.86	0.78, 0.93	-0.10	-0.16, -0.04	0.83	0.73, 0.93	
11	-0.08	-0.11, -0.04	0.86	0.79, 0.93	-0.10	-0.16, -0.05	0.83	0.73, 0.93	
12	-0.07	-0.10, -0.03	0.87	0.80, 0.95	-0.12	-0.17, -0.07	0.80	0.71, 0.90	

Table A2: Effect estimates on the additive scale (risk differences, RD) and multiplicative scale (risk ratios, RR) and their 95% confidence intervals (CIs) comparing dosing strategies {d1, d2} to the hybrid dose strategy d3 on risk of relapse across weeks 3-12 of treatment. Effect estimates given separately for BUP-NX treatment and for methadone treatment.

Wk.	BUP-NX				Methadone			
	RD		RR		RD		RR	
	$\hat{\psi}$	95% CI	$\hat{\psi}$	95% CI	$\hat{\psi}$	95% CI	$\hat{\psi}$	95% CI
<b>d1 vs. d3</b>								
3	-0.00	-0.00, 0.00	1.00	0.96, 1.04	0.00	-0.01, 0.01	1.00	0.93, 1.07
4	0.01	-0.01, 0.02	1.07	0.95, 1.19	0.01	-0.01, 0.02	1.04	0.91, 1.17
5	0.01	-0.01, 0.03	1.07	0.97, 1.18	0.00	-0.02, 0.02	1.02	0.90, 1.13
6	0.03	0.00, 0.05	1.08	1.01, 1.15	-0.00	-0.03, 0.03	1.00	0.92, 1.07
7	0.03	0.00, 0.06	1.09	1.02, 1.17	-0.00	-0.03, 0.03	0.99	0.92, 1.06
8	0.04	0.01, 0.07	1.11	1.05, 1.17	-0.01	-0.04, 0.02	0.98	0.92, 1.05
9	0.04	-0.00, 0.08	1.10	1.01, 1.19	-0.01	-0.04, 0.02	0.98	0.91, 1.05
10	0.02	-0.02, 0.06	1.05	0.97, 1.13	-0.00	-0.03, 0.03	1.00	0.93, 1.06
11	0.04	-0.00, 0.08	1.09	1.00, 1.17	0.01	-0.03, 0.04	1.01	0.94, 1.08
12	0.03	-0.01, 0.07	1.06	0.98, 1.14	0.02	-0.01, 0.06	1.04	0.97, 1.11
<b>d2 vs. d3</b>								
3	-0.00	-0.02, 0.01	0.98	0.71, 1.24	-0.01	-0.02, 0.00	0.92	0.84, 1.01
4	0.06	0.04, 0.08	1.56	1.40, 1.73	-0.01	-0.02, 0.00	0.94	0.85, 1.03
5	0.06	0.04, 0.08	1.34	1.22, 1.47	-0.01	-0.03, 0.00	0.92	0.80, 1.03
6	0.03	0.00, 0.05	1.08	1.01, 1.15	-0.01	-0.04, 0.02	0.97	0.91, 1.04
7	0.05	0.03, 0.07	1.15	1.09, 1.21	-0.02	-0.04, 0.01	0.96	0.91, 1.02
8	0.04	0.02, 0.07	1.11	1.05, 1.18	-0.00	-0.03, 0.02	0.99	0.94, 1.04
9	0.03	0.00, 0.06	1.08	1.01, 1.14	-0.01	-0.05, 0.03	0.97	0.89, 1.06
10	0.03	0.00, 0.06	1.07	1.01, 1.14	-0.00	-0.03, 0.03	0.99	0.93, 1.05
11	0.04	0.01, 0.07	1.09	1.03, 1.16	-0.00	-0.04, 0.04	1.00	0.92, 1.08
12	0.04	0.00, 0.07	1.08	1.01, 1.14	0.01	-0.03, 0.04	1.01	0.94, 1.09

Table A3: Number of patients randomized to receive BUP-NX and methadone that were observed as having dose increased, but did not increase dose under a given treatment strategy.

	Wk. 2	3	4	5	6	7	8	9	10	11
<b>BUP-NX</b>										
Dynamic	171	99	75	43	37	24	17	14	9	9
Threshold	237	125	90	43	38	26	17	15	9	8
Hybrid	136	86	60	33	30	22	13	11	7	6
<b>Methadone</b>										
Dynamic	117	96	79	63	53	41	43	28	30	31
Threshold	17	30	37	30	24	24	26	22	22	31
Hybrid	8	16	26	21	18	19	21	18	15	21

Table A4: Proportion of patients randomized to receive BUP-NX and methadone that met components of treatment strategy *eligibility* for having dose increased under a given treatment strategy.

	Wk. 2	3	4	5	6	7	8	9	10	11
<b>BUP-NX</b>										
Prior week use	0.43	0.28	0.23	0.12	0.11	0.10	0.11	0.08	0.07	0.07
Dose under threshold	0.84	0.70	0.64	0.55	0.52	0.49	0.47	0.44	0.42	0.41
<i>CTN0027</i>										
Prior week use	0.53	0.30	0.24	0.09	0.08	0.08	0.08	0.07	0.05	0.07
Dose under threshold	0.74	0.53	0.47	0.37	0.34	0.33	0.30	0.28	0.27	0.26
<i>CTN0030</i>										
Prior week use	0.36	0.32	0.26	0.19	0.15	0.13	0.16	0.09	0.10	0.10
Dose under threshold	0.93	0.86	0.82	0.72	0.69	0.66	0.64	0.61	0.59	0.59
<i>CTN0051</i>										
Prior week use	0.24	0.19	0.17	0.10	0.12	0.10	0.12	0.10	0.08	0.07
Dose under threshold	0.99	0.91	0.86	0.79	0.75	0.71	0.67	0.63	0.60	0.58
<b>Methadone</b>										
Prior week use	0.51	0.43	0.37	0.14	0.12	0.11	0.10	0.09	0.10	0.09
Dose under threshold	0.88	0.81	0.77	0.56	0.53	0.51	0.49	0.47	0.45	0.44

Table A5: Maximum density ratio used in the weights of the sequentially doubly robust estimator by medication type, dosing strategy, and week of treatment.

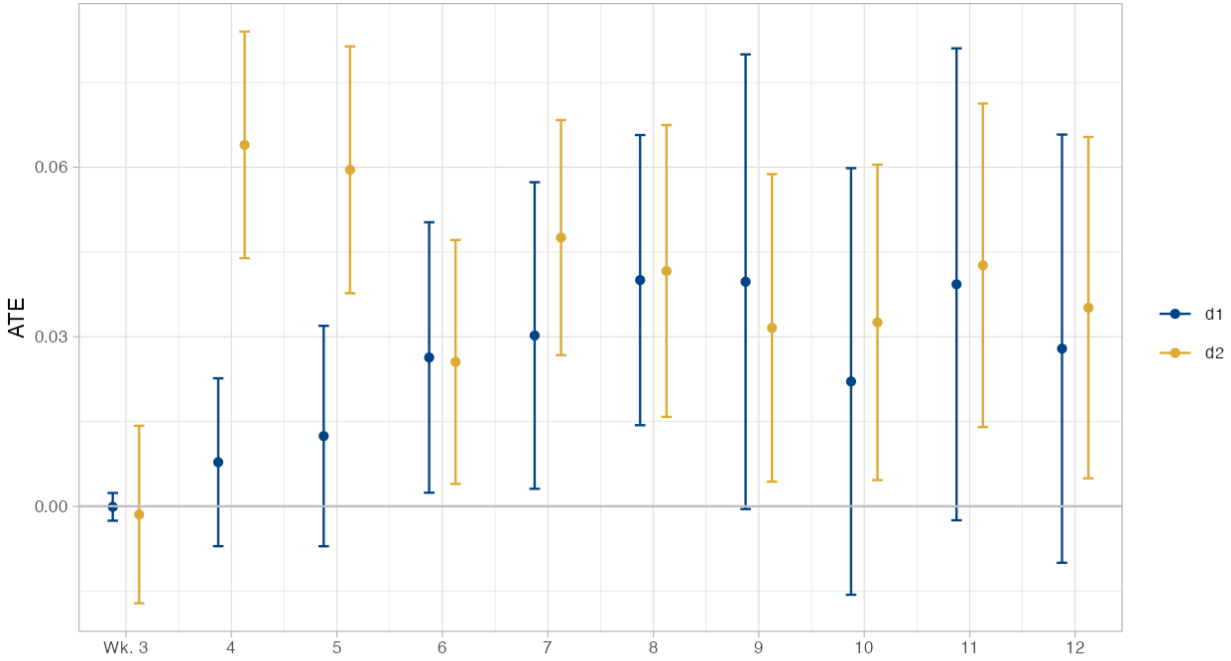
	Wk. 2	3	4	5	6	7	8	9	10	11
<b>BUP-NX</b>										
d4	1.45	1.39	1.27	1.23	1.11	1.08	1.07	1.04	1.03	1.07
d1	3.21	5.67	5.21	7.88	6.98	17.61	16.62	17.61	17.61	17.61
d2	5.01	3.91	7.40	7.07	7.40	7.02	7.40	6.07	7.40	7.35
d3	3.44	4.11	3.60	3.44	6.40	7.36	7.73	7.73	7.73	7.73
<b>Methadone</b>										
d4	3.73	3.20	2.21	1.82	1.55	1.40	1.28	1.25	1.21	1.29
d1	1.81	4.31	2.18	3.94	1.51	2.96	1.01	2.62	4.31	1.01
d2	4.46	7.27	3.96	5.10	2.03	2.36	4.29	7.75	2.36	7.75
d3	1.68	3.91	2.56	3.91	2.20	1.51	1.95	2.19	2.12	2.25

Table A6: Number of patients randomized to receive BUP-NX, stratified by trial, that were observed as following a given strategy: (1) increased dose under the strategy and were observed as increasing dose, or (0) had a constant dose under the strategy and were observed as having a constant dose.

	Wk. 2	3	4	5	6	7	8	9	10	11
Constant dose strategy, d4										
<b>CTN0027</b>										
<i>Total</i>	549	569	429	406	325	314	306	281	259	248
<b>CTN0030</b>										
<i>Total</i>	290	320	303	311	277	265	259	253	246	240
<b>CTN0051</b>										
<i>Total</i>	189	220	215	211	199	200	183	176	170	159
Increase dose in response to use strategy, d1										
<b>CTN0027</b>										
Increase	92	33	25	13	3	2	2	2	3	1
Constant	265	317	296	302	272	270	258	237	227	212
<b>CTN0030</b>										
Increase	32	15	12	6	3	3	3	0	0	1
Constant	195	213	219	221	222	214	207	216	213	210
<b>CTN0051</b>										
Increase	23	11	3	5	5	1	2	2	1	1
Constant	145	172	170	175	167	168	149	149	149	138
Increase dose if under threshold strategy, d2										
<b>CTN0027</b>										
Increase	26	11	8	4	1	1	2	1	1	2
Constant	413	432	351	337	272	268	262	243	227	219
<b>CTN0030</b>										
Increase	8	5	3	1	2	0	1	0	0	1
Constant	190	220	215	228	196	185	179	175	167	164
<b>CTN0051</b>										
Increase	33	10	10	8	6	2	3	2	2	1
Constant	92	118	130	134	129	131	120	118	116	107
Hybrid dosing strategy, d3										
<b>CTN0027</b>										
Increase	99	38	28	16	4	3	4	3	3	3
Constant	230	274	259	261	234	233	226	212	204	191
<b>CTN0030</b>										
Increase	35	17	14	7	5	3	3	0	0	1
Constant	122	147	155	158	151	145	145	148	139	141
<b>CTN0051</b>										
Increase	48	17	13	11	9	3	5	4	3	2
Constant	71	90	99	108	107	110	94	97	100	92

Figure A2: Estimated average treatment effects (with 95% confidence intervals), comparing dosing strategies  $d \in \{d1, d2\}$  to the hybrid strategy ( $d3$ ), among (a) patients randomized to BUP-NX and (b) patients randomized to methadone.

(a) BUP-NX



(b) Methadone

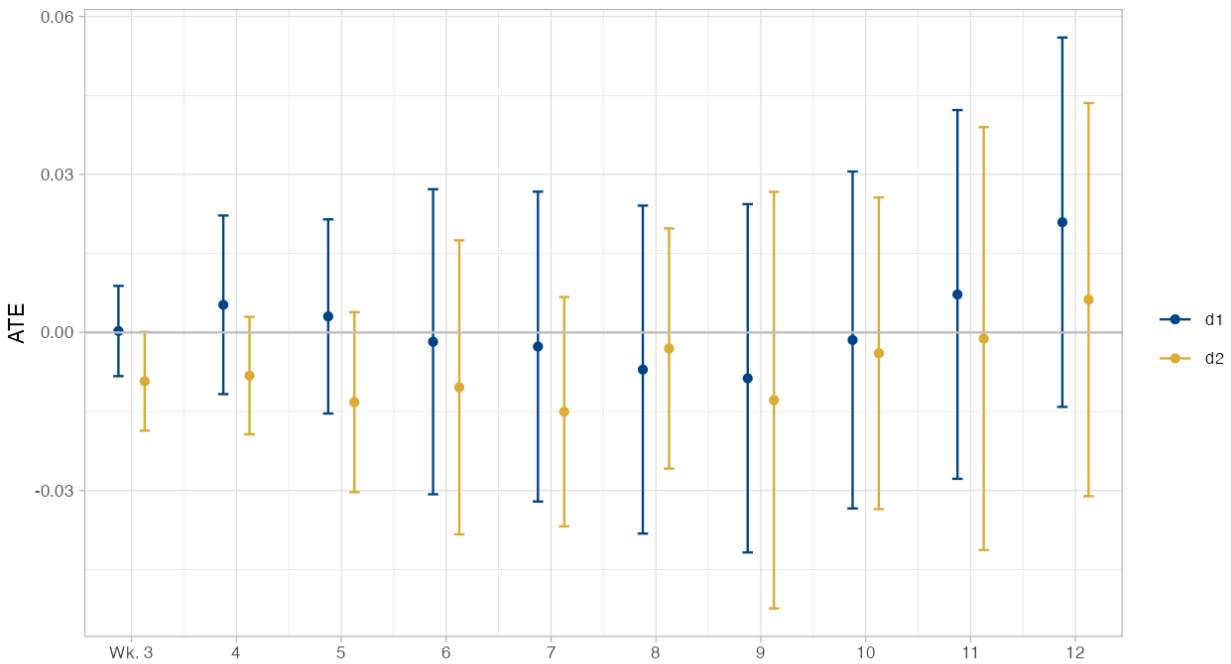


Figure A3: Estimated marginal risks of relapse and average treatment effects (with 95% confidence intervals), comparing dosing strategies  $d \in \{d1, d2, d3\}$  to the reference of constant dose ( $d4$ ), among patients randomized to BUP-NX in trial CTN0027.

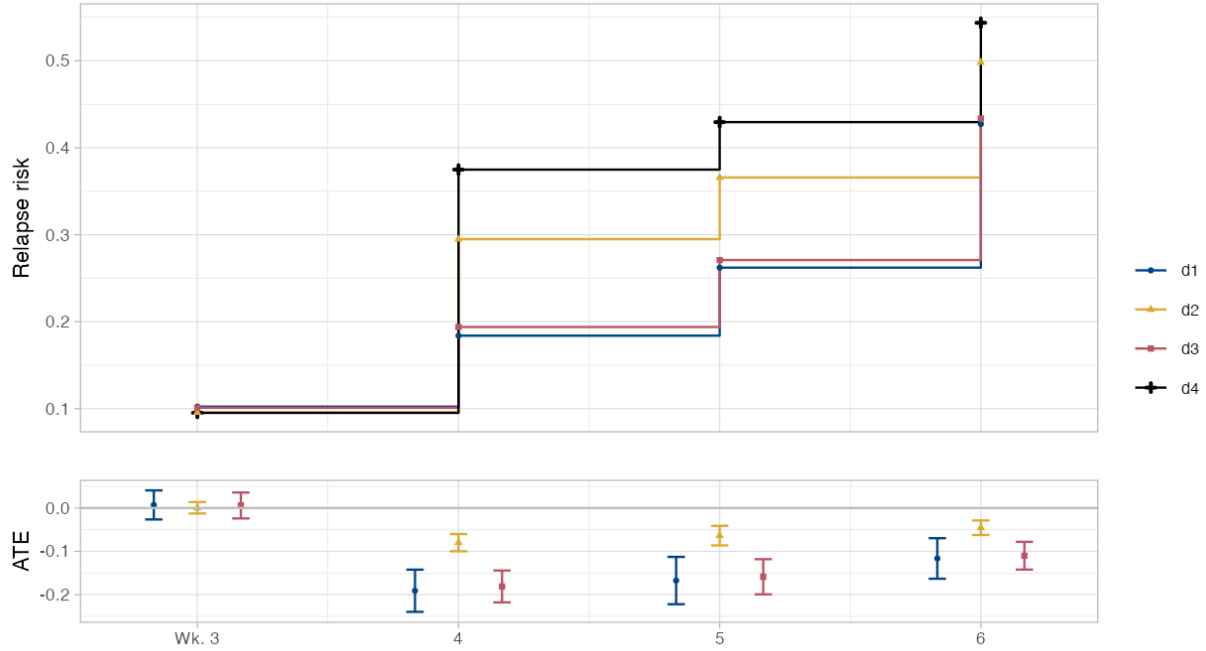


Figure A4: Estimated marginal risks of relapse and average treatment effects (with 95% confidence intervals), comparing dosing strategies  $d \in \{d1, d2, d3\}$  to the reference of constant dose ( $d4$ ), among patients randomized to BUP-NX in trial CTN0030.

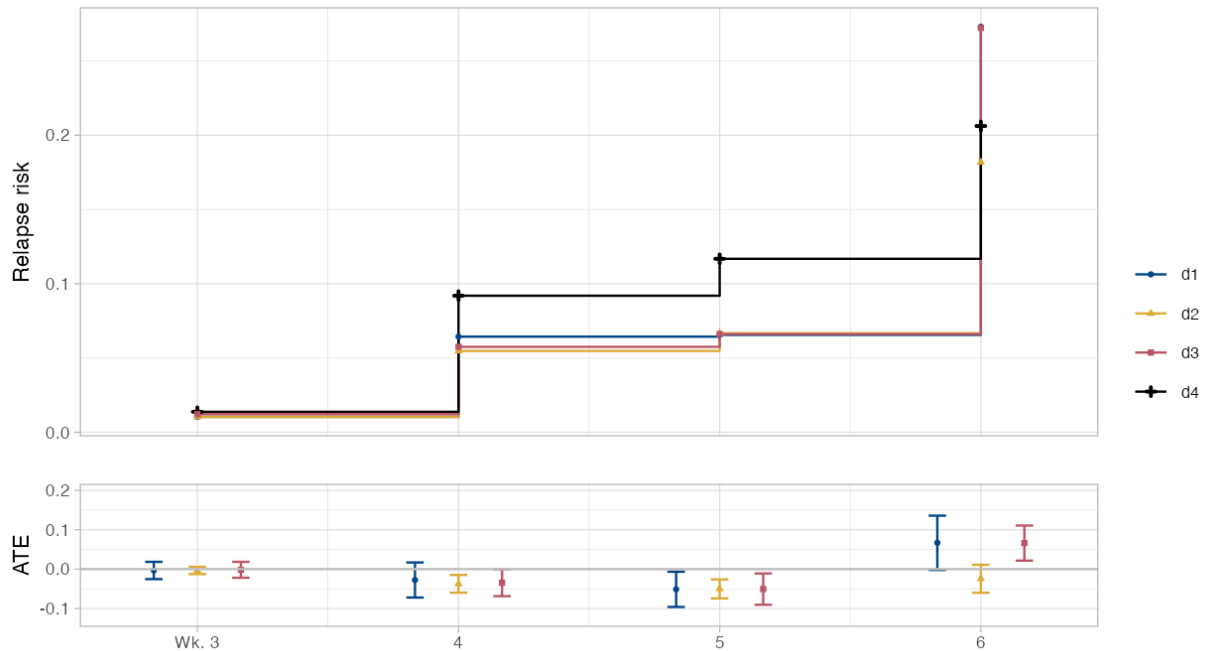
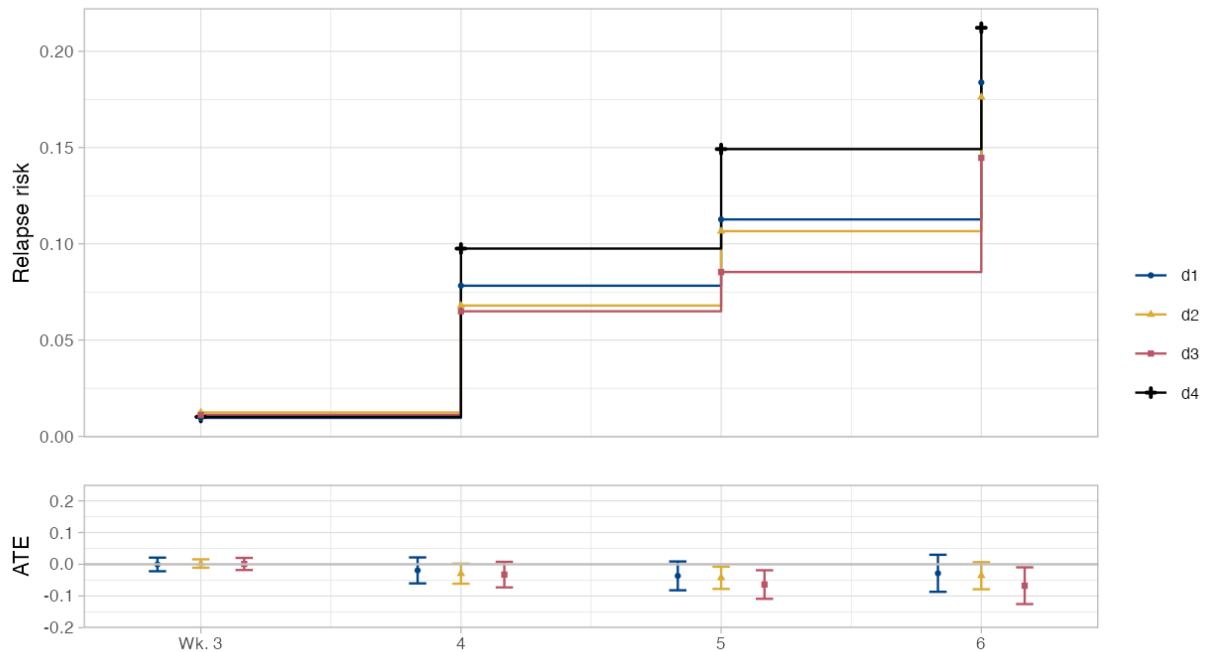




Figure A5: Estimated marginal risks of relapse and average treatment effects (with 95% confidence intervals), comparing dosing strategies  $d \in \{d1, d2, d3\}$  to the reference of constant dose ( $d4$ ), among patients randomized to BUP-NX in trial CTN0051.



## References

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