Is *Grass* Greener in the Gray Zone? Legalization and Innovation in the *Cannabis* Market

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(https://ssrn.com/abstract=4373615)

| **Introduction** | Institutions and Data | Clinical Trials | Patents | Global Sample | Conclusion |
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Motivation

Barriers to innovation are high in restricted/illicit market

- Innovation is essential for economic growth, yet competitive markets under-incentivize innovation (Nelson 1959; Arrow 1962)

- Institutions (e.g., org., laws) play a key complementary role to market incentives in spurring innovation by ...
    - enhancing knowledge diffusion & reducing costs (Moser 2005; Furman & Stern 2011; Williams 2013; Murray et al. 2016; Wang 2022)

- Barriers to innovation are higher in **restricted/illicit** markets
    - Stem cells (Gershon 2003; Furman et al. 2012), cryptocurrencies (Chohan 2017), and nuclear power (Reinhardt 2008)
    - Legal institutions are key to set standards and direct innovation

- Q: How would legal institutions affect the rate & direction of innovation in such markets? (esp. to learn about the cost of R&D?)

1

The growing cannabis market and lingering controversies

- Cannabis is the most widely used drug globally
  - Estimated 209m global consumers in 2020 (UNODC 2022)
  - 48.2m Americans (18% of the pop.) used in 2019 (SAMHSA 2019)
  - Global legal cannabis market is estimated at $100.4+b by 2026

- Once widely prohibited, cannabis has been widely legalized
  - Medical/adult-use cannabis has been legalized in 50+ countries
  - Still the most widely trafficked and abused illicit drug (WHO)
  - US: federally illegal but been *patented* by the fed. (HHS, 2003)

- In principle, policymakers who love/hate cannabis would like to have +/- evidence; in practice, we have *little* evidence

Research Q: legalization and innovation in a gray market

Does legalization affect innovation in the cannabis market?

- Document the trends of R&D in the cannabis market
    - Cannabis-related clinical trials & patent applications

- Estimate the causal effects of cannabis legalization
    - Differentiate medical vs adult-use cannabis legalization

- Examine heterogeneity of policy responses and mechanisms
    - R&D responses in different categories (upstream/downstream)

Overall: the first empirical analysis on legalization and the rate and direction of innovation in the cannabis market (US & global)

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Institutions and Data
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Patents
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Global Sample
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Conclusion
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Science, History, and Research Barriers

- Cannabis: 2 main species: Indica & Sativa,+hybrid strains
  - 100+ compounds found in cannabis (i.e., cannabinoids)
  - esp: cannabidiol (CBD) and tetrahydrocannabinol (THC)
  - non-cannabinoids (e.g., terpenes, flavonoids) can affect therapeutic fcns

- History: prohibition began in 1910s (after decades of relative permissiveness)
  - 60-90s: ∼ global consensus, UN Convention, "War on Drugs"
  - 1990s-: federal & state laws diverge (90s CA, treat AIDS patients, e.g., pain)
  - 2018.12 US farm bill, Covid "essential", 2020 ECJ&UN rules

- US schedule I controlled substances (highly addictive, no med values)
  - clinical research w cannabis: sep. approvals from FDA & DEA
  - obtain cannabis from U Mississippi (NIDA contract); not from disp.

4

Introduction	Institutions and Data	Clinical Trials	Patents	Global Sample	Conclusion
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Quantitative Methods

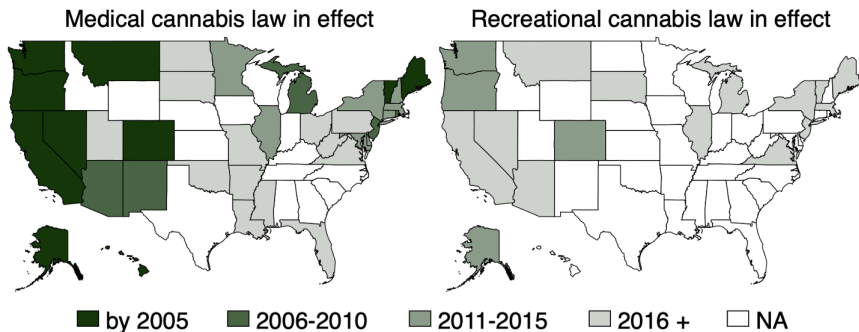# Empirical strategy & specification: benchmark

- Diff-in-Diff: common trends & lack of common shocks
    - Compare outcomes in states/countries that legalized cannabis earlier to these legalized later or not (yet) legalized

$$y_{st} = \beta MedCL_{st} + \gamma RecCL_{st} + \delta_s + \delta_t + \varepsilon_{st}$$

- y_{st}: # clinical trials, # patent filings (total & by category); ihs/pr./log
- $MedCL_{st}/RecCL_{st}$: medical/recreational cannabis law in effect
- $\delta_s + \delta_t$: fixed effects at the state & year levels (US sample)
- Corroborate results w/ recent DiD methods (Goodman-Bacon 2021; Callaway & Sant'Anna 2021, Roth 2022) and count data models
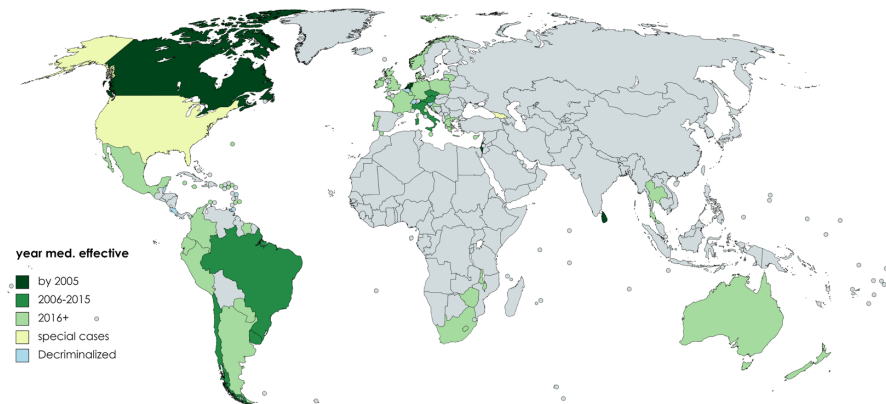- Then, repeat at the country-year level (by origin/target country)

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Quantitative Methods

Cannabis legalization across states in the US (by 2021.5.12)

- 2023.3: MedCLs in 37 states+DC; RecCLs in 21 states+DC

Medical cannabis law in effect

Recreational cannabis law in effect

■ by 2005   ■ 2006-2010   ■ 2011-2015   □ 2016 +   □ NA

US policies

Introduction	Institutions and Data	Clinical Trials	Patents	Global Sample	Conclusion
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Quantitative Methods

Cannabis-related laws/policies are fast evolving globally

- Medical cannabis: effectively legalized in 50 countries/territories
  - US & GE special; decriminalized in 7 more countries (by 2021.5.14)

year med. effective
- by 2005
- 2006-2015
- 2016+
- special cases
- Decriminalized

▸ global policies

Introduction	Institutions and Data	**Clinical Trials**	Patents	Global Sample	Conclusion
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Data

Cannabis-related clinical trials: data & overview

- Upstream clinical trials can focus on up-/down-stream issues
  - ClinicalTrials.gov: US registry for global trials (<40% US trials)

- Procedure: identify & extract any cannabis-related conditions
  - Start w the broadest set, code manual check false inclusions

- Geography info: collected from trial site location section, or backed up from trial description, trial-linked sources or related publications

  Final sample:

- 856 US-registered cannabis trials 2000-2020 (559 US-based trials)
- $\sim$ 80% in a single state, $\sim$ 10% in two states, $\sim$ 10% in 2+ states
- funding: 6% industry, 47% NIH/fed, 92% others (48% solely others)
- decentralized: mostly by researchers in universities/hospitals/centers

Introduction ○○○ | Institutions and Data ○○○○ | **Clinical Trials** ○●○ | Patents ○○○○○ | Global Sample ○ | Conclusion ○

Descriptives

Clinical trials: trends across categories (i.e., focus areas)

- Categorize cannabis-related clinical trials into: +/neutral/- groups

Trial category	Descriptions/examples
Treatment	Efficacy of cannabis products on patients with certain conditions
Usage/effects	Usage, effects on the body, and function of cannabis receptors
Abuse factors	Abuse and dependence, including risk factors for abuse

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Results
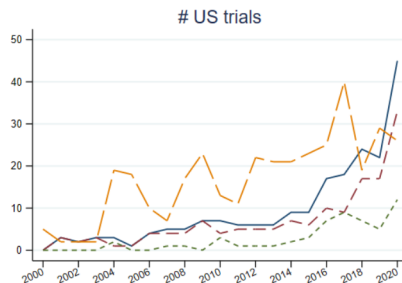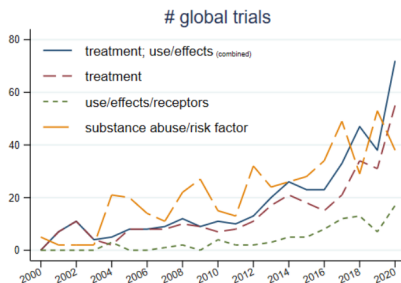
US trials increase mildly after RCLs but not MCLs

outcome	(1) total	(2) treatment	(3) use/effect	(4) abuse
Panel A: number of clinical trials				
MedCL	0.164	0.107	0.0531	0.00373
	(0.203)	(0.0802)	(0.0466)	(0.125)
RecCL	0.905**	0.434**	0.0438	0.427**
	(0.369)	(0.195)	(0.0775)	(0.205)
LHS mean	0.801	0.211	0.052	0.537
Panel B: log number of clinical trials				
MedCL	0.0476	0.0492	0.0271	0.0115
	(0.0658)	(0.0387)	(0.0256)	(0.0549)
RecCL	0.276**	0.220**	0.0302	0.155**
	(0.111)	(0.0949)	(0.0489)	(0.0736)
LHS mean	0.387	0.123	0.033	0.294

▸ event study   ▸ (by cat.)   ▸ Bacon decomp. (fig)   ▸ (tab)   ▸ Callaway & Sant'Anna   ▸ Roth test

RCL results are consistent with anecdotes on creative use of dispensaries; also in line with wider access to more cannabis users for trial recruitment

10

Cannabis-related patents applications: data & overview

- Patent eligible! US HHS received a cannabis patent in 2003
    - Eligible for all: utility patent, plant patent, & design patent...

- Identify relevant patents from by titles & abstracts text
    - Adjustment for value: weighted counts by DOCDB family size

- Categorize based on content (textual analyses+manual code)

- Following recent literature on inventor geo-coding techniques

▸ PATSTAT data construction (logic graph) ▸ US HHS 2003 cannabis patent

Cannabis-related patent applications: categorization

| Patent category	Descriptions/examples
Chemical	Chemicals related to cannabis or cannabinoid system
	Chemicals obtained from cannabis, cannabinoid system, or chemical reaction
	Cannabis-related chemicals preparation, composition, or formulation
	Chemicals acting on/with cannabinoid or cannabinoid receptor
	Chemicals analogs to cannabis molecule or compounds
	Chemicals related to cannabis or cannabis system
Medical use	Chemical formulation or technology for medical use
	Chemicals containing cannabis substance for medical use
	Chemicals/technology acting on cannabinoid receptor for medical use
	Chemicals acting on/with cannabinoid for medical use
	Treatment address cannabis side effects, toxicity, dependence, or abuse
Method	Agricultural/industrial/business methods pertaining to cannabis
	Methods for production, extraction, synthesis, or processing substances
	Methods for analysis, administration, testing, detection, measurement
	Methods for identification of cannabis or related substances
Product	Products or facilities for cultivation or production; equipment and devices
	Cannabis-related inputs to agricultural/industrial production or business
	Consumer products (e.g., edibles, beverages) or devices (e.g., vaporizers)

Cannabis-related US patent filings rise more substantially

- The figures include all US cannabis patent filings; the analyses focus on US filings by US-based inventors (state info identified)
- # applications: 1,706 US patents, 12,641 global patents, 2000-2019
- very decentralized in filings; vast majority are utility patents (99%)
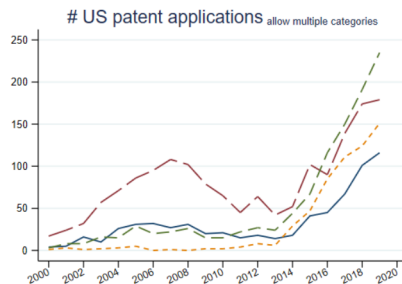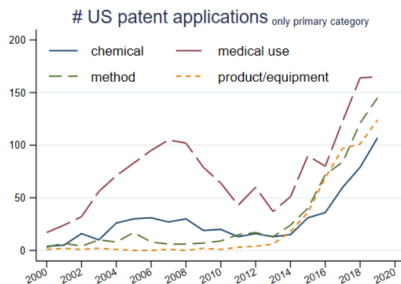
Cannabis-related US patent filings rise, esp. post RCLs

- Sharp distinction btw MCL vs. RCL responses in patenting
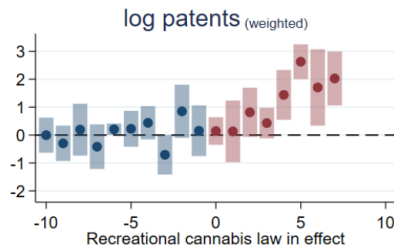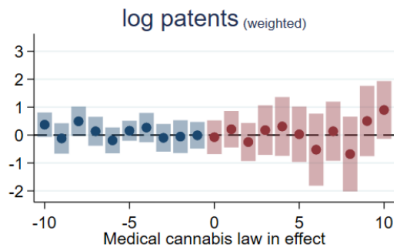
Patent filings rise, mainly in non-med., downstream areas

outcome	(1) total	(2) chemical	(3) medical	(4) method	(5) product
Panel A: log patent applications					
MedCL	0.00332	-0.0463	0.0329	0.0973	0.101
	(0.159)	(0.0901)	(0.143)	(0.0797)	(0.0793)
RecCL	0.921***	0.370*	0.364**	0.865***	0.749***
	(0.218)	(0.197)	(0.162)	(0.178)	(0.209)
LHS mean	0.643	0.212	0.389	0.193	0.140
Panel B: log quality-weighted patent applications					
MedCL	0.0142	-0.140	0.0851	0.270*	0.232*
	(0.284)	(0.203)	(0.281)	(0.161)	(0.120)
RecCL	1.232***	0.660*	0.671**	1.410***	1.312***
	(0.357)	(0.389)	(0.314)	(0.297)	(0.316)
LHS mean	1.217	0.466	0.807	0.352	0.221
Observations	940	940	940	940	940

▸ event study (overall) ▸ (RCL, by group) ▸ Bacon decomp. (fig) ▸ (table)

▸ Callaway & Sant'Anna (MCL) ▸ Callaway & Sant'Anna (RCL) ▸ Roth test

Results are robust to other tests and count data models

15

Cannabis-related R&D in the global landscape

- US-registered non-US trials are limited; many ex-US patents
  - aggregate patent country by: 1) origin: inventor country, 2) target: jurisdiction of patent application
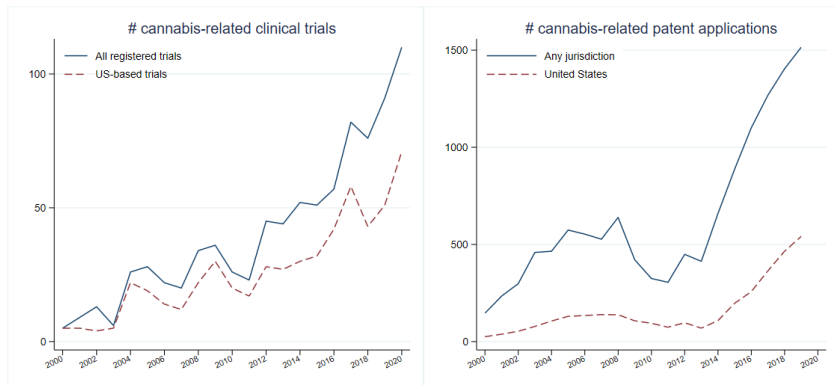
Global patent filings respond significant to:
1) RCLs in the countries of origin and 2) MCLs in the target countries

Conclusion & Discussion

- Legalization increases R&D, but not enough medical R&D
  - Trials increase mildly after RCLs, but not after MCLs
  - More patenting post RCLs, but mainly downstream-oriented

- Cannabis legalization (for adult-use) increases innovation, but not naturally and not enough in where it matters the most

- 2022.12: Medical Marijuana and Cannabidiol Research Expansion Act enacted to reduce barriers to cannabis research
  - worth more future studies in this direction

Appendix TOC

- Legalization years
- Scientific background
- US HHS 2003 pot patent
- PATSTAT logic graph
- Global sample results
- Event studies (regular)
- Goodman-Bacon (2021) decomposition (Table)
- Event studies (Callaway & Sant'Anna 2021)
- Roth (2022) test on power of pre-trends
- Other specifications

Cannabis legalization: US state implementation years

State	MCL	RCL	State	MCL	RCL
Alaska	1999	2015	Montana	2004	2021
Arizona	2010	2020	Nevada	2001	2017
Arkansas	2016		New Hampshire	2013	
California	1996	2016	New Jersey	2010	2021
Colorado	2000	2012	New Mexico	2007	
Connecticut	2012		New York	2014	2021
Delaware	2011		North Dakota	2016	
District of Columbia	2010	2015	Ohio	2016	
Florida	2017		Oklahoma	2018	
Hawaii	2000		Oregon	1998	2015
Illinois	2014	2020	Pennsylvania	2016	
Louisiana	2016		Rhode Island	2006	
Maine	1999	2017	South Dakota	2021	2021
Maryland	2014		Utah	2018	
Massachusetts	2013	2016	Vermont	2004	2018
Michigan	2008	2018	Virginia	2020	2021
Minnesota	2014		Washington	1998	2012
Mississippi	2021		West Virginia	2019	
Missouri	2018				

2

Cannabis legalization: global implementation years

Country	MCL	RCL	Country	MCL	Country	MCL
Canada	2001	2018	Denmark	2018	Norway	2018
Georgia		2018	Ecuador	2020	Paraguay	2018
Uruguay	2014	2014	Germany	2017	Peru	2019
Antigua and Barbuda	2019		Gibraltar	2019	Poland	2017
Argentina	2017		Greece	2018	Portugal	2018
Aruba	2019		Ireland	2019	Puerto Rico	2016
Australia	2016		Israel	1999	North Macedonia	2016
Austria	2008		Italy	2007	Saint Kitts and Nevis	2019
Barbados	2020		Jamaica	2016	St Vincent & the Grenadines	2019
Bermuda	2016		Lesotho	2018	San Marino	2016
Brazil	2015		Lithuania	2019	South Africa	2018
Cayman Islands	2017		Luxembourg	2018	Sri Lanka	1961
Chile	2015		Malawi	2020	Suriname	2020
Colombia	2016		Malta	2018	Thailand	2019
Croatia	2016		Mexico	2017	United Kingdom	2018
Cyprus	2019		Netherlands	2003	Zimbabwe	2019
Czechia	2014		New Zealand	2020		

Scientific background: commonly used cannabis medicines

- *Cannabis*: has 2 main species: Indica & Sativa,+hybrid strains
  - Cannabidiol (CBD) and tetrahydrocannabinol (THC)

legacy medicines	new medicines

Marinol (dronabinol, a synthetic THC**)**

Cesamet (nabilone, a synthetic cannabinoid similar to THC**)**

USFDA approved both in 1985

Bedrocan
Standardized dosage medical cannabis; heated and smoked or taken orally [not US-approved]

Sativex (nabiximols)
(THC & CBD in 1:1 ratio)

UK approval in 2010 [not FDA-approved in the US]

Epidiolex
(plant-derived CBD)

USFDA approval in 2018

- Only three FDA-approved products, one derived from cannabis

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4

The first US cannabis patent held by HHS

(12) **United States Patent**
Hampson et al.

(10) Patent No.: **US 6,630,507 B1**
(45) Date of Patent: **Oct. 7, 2003**

(54) **CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS**

(75) Inventors: **Aidan J. Hampson**, Irvine, CA (US);
Julius Axelrod, Rockville, MD (US);
Maurizio Grimaldi, Bethesda, MD (US)

(73) Assignee: **The United States of America as represented by the Department of Health and Human Services**, Washington, DC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/674,028**

(22) PCT Filed: **Apr. 21, 1999**

(86) PCT No.: **PCT/US99/08769**

§ 371 (c)(1),
(2), (4) Date: **Feb. 2, 2001**

(87) PCT Pub. No.: **WO99/53917**

PCT Pub. Date: **Oct. 28, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/082,589, filed on Apr. 21, 1998, and provisional application No. 60/095,993, filed on Aug. 10, 1998.

(57) **ABSTRACT**

Cannabinoids have been found to have antioxidant properties, unrelated to NMDA receptor antagonism. This new found property makes cannabinoids useful in the treatment and prophylaxis of wide variety of oxidation associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases. The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV dementia. Nonpsychoactive cannabinoids, such as cannabidoil, are particularly advantageous to use because they avoid toxicity that is encountered with psychoactive cannabinoids at high doses useful in the method of the present invention. A particular disclosed class of cannabinoids useful as neuroprotective antioxidants is formula (I) wherein the R group is independently selected from the group consisting of H, CH$_3$, and COCH$_3$.
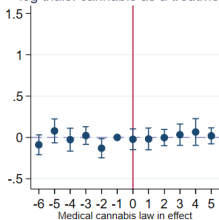
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5

Patent data construction: PATSTAT logic graph

6
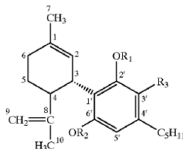
Event studies: cannabis-related clinical trials, overall
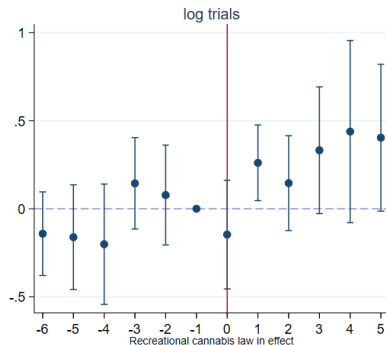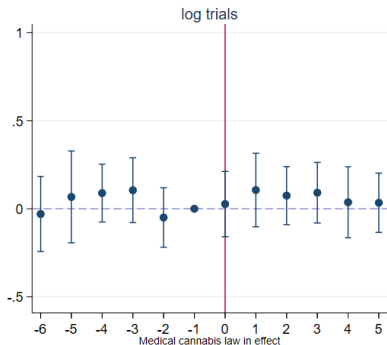
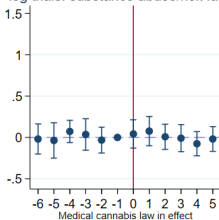# Event studies: cannabis-related clinical trials, by category
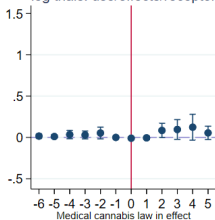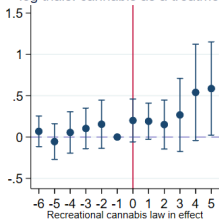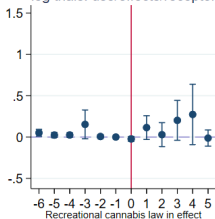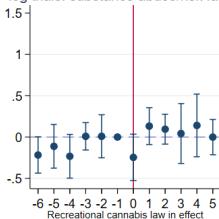
Event studies: cannabis-related patents, overall
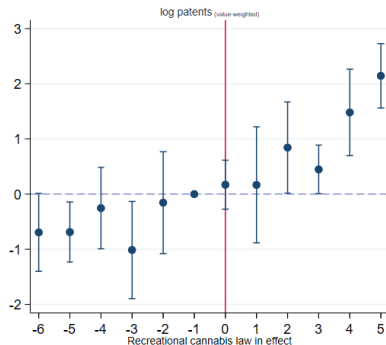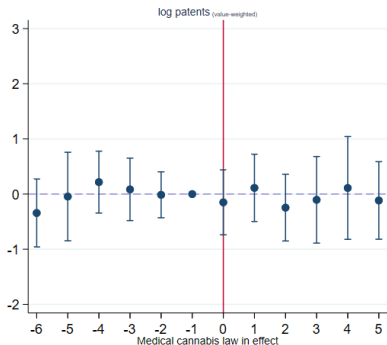
Event studies: cannabis-related patents, RCL, by category
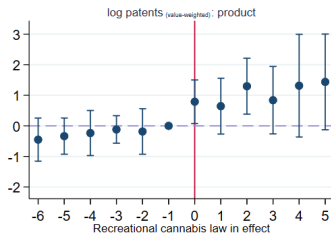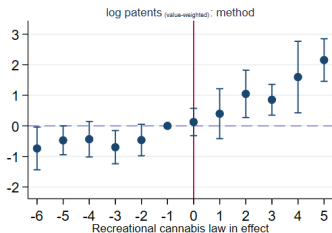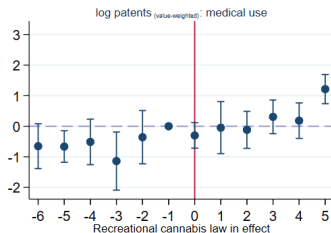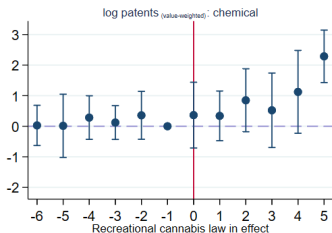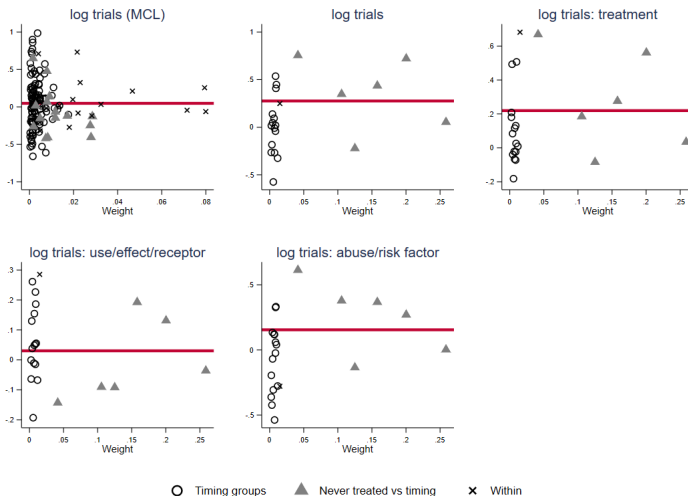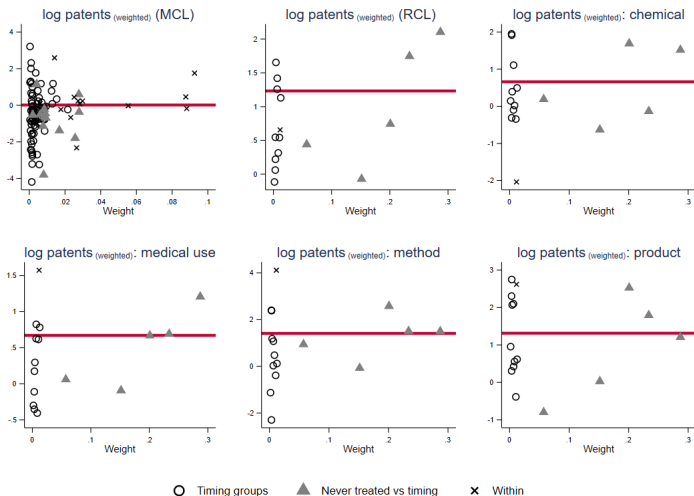
Goodman-Bacon (2021) decomposition figures: trials

○ Timing groups ▲ Never treated vs timing ✕ Within

Goodman-Bacon (2021) decomposition figures: patents

Goodman-Bacon (2021) decomposition results

outcomes	coeff.	weight	coeff.	weight	coeff.	weight	coeff.	weight
	trials (MCL)		trials (RCL)		patents (MCL)		patents (RCL)	
Timing Groups	0.046	0.342	0.043	0.096	-0.334	0.311	0.830	0.058
Never vs Timing	0.086	0.472	0.301	0.889	0.331	0.521	1.264	0.931
Within	1.767	0.007	0.250	0.015	7.827	0.005	0.658	0.011
Always vs Timing	-0.155	0.176			-0.737	0.161		
Always vs Never	2.293	0.003			10.964	0.002		

trials (RCL)	treatment		use/effect/receptor		abuse/risk factor	
Timing Groups	0.078	0.096	0.058	0.096	-0.028	0.096
Never vs Timing	0.227	0.889	0.023	0.889	0.182	0.889
Within	0.683	0.015	0.286	0.015	-0.277	0.015

patents (RCL)	chemical		medical		method		product	
Timing Groups	0.387	0.058	0.375	0.058	0.341	0.058	0.874	0.058
Never vs Timing	0.710	0.931	0.679	0.931	1.444	0.931	1.324	0.931
Within	-2.032	0.011	1.578	0.011	4.123	0.011	2.623	0.011

13

Callaway and Sant'Anna (2021) estimates: trials
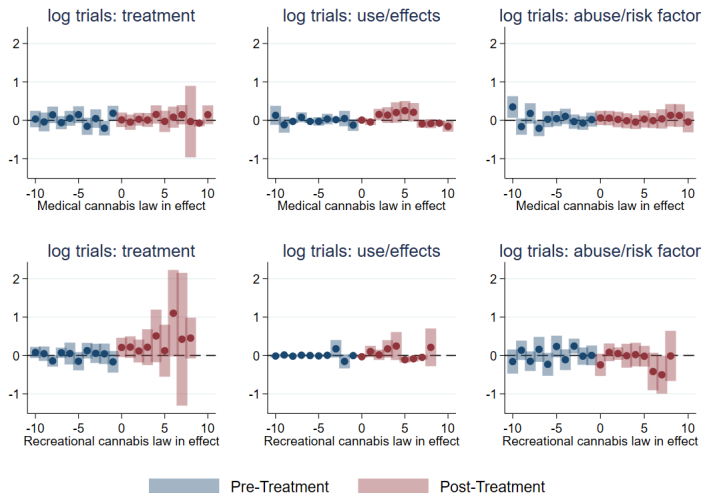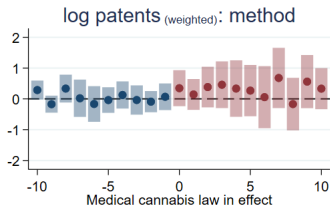
Callaway and Sant'Anna (2021) MCL estimates: patents

◂ back (patents)

Callaway and Sant'Anna (2021) RCL estimates: patents

log patents (weighted): chemical — log patents (weighted): medical use — log patents (weighted): method — log patents (weighted): product

Recreational cannabis law in effect
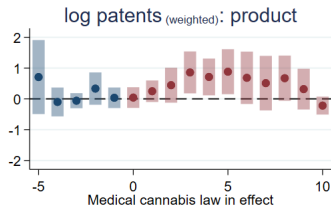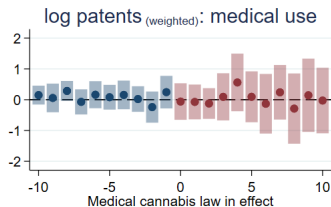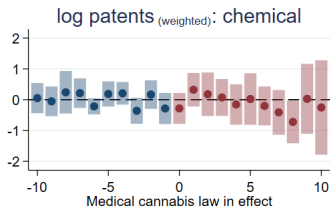
Pre-Treatment — Post-Treatment
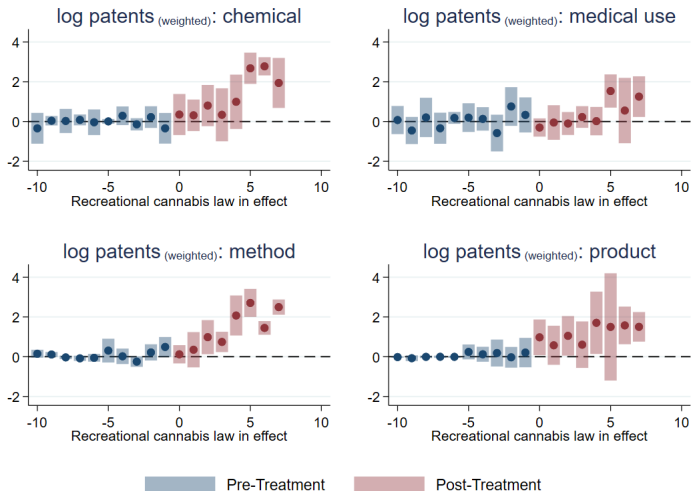
Pre-trend power tests à la Roth (2022)

	(1)	(2)	(3)	(4)	(5)
Panel A: log number of clinical trials					
	total	treatment	use/effect	abuse	
β	0.276**	0.220**	0.0302	0.155**	
$\gamma_{0.5}$	0.043	0.035	0.006	0.036	
$\gamma_{0.8}$	0.065	0.052	0.010	0.057	
Panel B: log quality-weighted patent applications					
	total	chemical	medical	method	product
β	1.232***	0.660*	0.671**	1.410***	1.312***
$\gamma_{0.5}$	0.104	0.128	0.101	0.100	0.130
$\gamma_{0.8}$	0.161	0.186	0.158	0.151	0.192

Global results: cannabis-related clinical trials

	(1)	(2)	(3)	(4)
Panel A: log number of clinical trials				
	total	treatment	use/effect	abuse
MedCL	-0.111	-0.0214	-0.0724	-0.119**
	(0.0759)	(0.0634)	(0.0475)	(0.0526)
RecCL	1.795***	1.703***	0.881***	0.939***
	(0.0716)	(0.0627)	(0.0485)	(0.0539)
LHS mean	0.270	0.160	0.040	0.140
N obs.	966	966	966	966

Global results: cannabis-related patent filings

	(1)	(2)	(3)	(4)	(5)
Panel B: log number of patent applications (weighted) in origin country				
	total	chemical	medical	method	product
MedCL	0.0298	-0.178	-0.00245	0.0856	0.320
	(0.471)	(0.327)	(0.349)	(0.296)	(0.232)
RecCL	0.561*	0.727***	-0.438	0.996**	0.253
	(0.295)	(0.272)	(0.421)	(0.392)	(0.843)
LHS mean	2.020	1.048	1.497	0.632	0.330
N obs.	1,400	1,400	1,400	1,400	1,400
Panel C: log number of patent applications (weighted) in target country				
	total	chemical	medical	method	product
MedCL	0.837***	0.487*	0.285	0.733***	0.838***
	(0.313)	(0.251)	(0.293)	(0.204)	(0.193)
RecCL	0.178	0.316*	-0.531	0.228	-0.548
	(0.422)	(0.174)	(0.584)	(0.395)	(0.979)
LHS mean	3.062	1.970	2.512	1.348	0.645
N obs.	2,300	2,300	2,300	2,300	2,300

Global results in alternative, focused samples

	(1) total	(2) chemical	(3) medical	(4) method	(5) product
Panel A: log number of patent applications in origin country					
Sample 1: exclude RCL countries					
MedCL	0.0511	-0.184	0.0416	0.0462	0.406*
	(0.502)	(0.348)	(0.372)	(0.314)	(0.236)
Sample 2: exclude RCL countries, US, and China					
MedCL	0.100	-0.157	0.0804	0.102	0.508**
	(0.505)	(0.351)	(0.373)	(0.315)	(0.228)
Panel B: log number of patent applications in target country					
Sample 1: exclude RCL countries					
MedCL	0.909***	0.527**	0.354	0.740***	0.933***
	(0.325)	(0.263)	(0.304)	(0.214)	(0.189)
Sample 2: exclude RCL countries, US, and China					
MedCL	0.940***	0.545**	0.378	0.765***	0.977***
	(0.325)	(0.263)	(0.304)	(0.214)	(0.188)