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A systematic review of methamphetamine precursor regulations

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ABSTRACT

Aims To assess the effectiveness of methamphetamine precursor regulations in reducing illicit methamphetamine supply and use. **Methods** A systematic review of 12 databases was used to identify studies that had evaluated the impact of methamphetamine precursor regulations on methamphetamine supply and/or use. The guidelines of the Effective Practice and Organization of Care Group (EPOC) of The Cochrane Collaboration were used to determine which study designs were included and assess their quality. **Results** Ten studies met the inclusion criteria. These studies evaluated 15 interventions (13 regulations and two related interdiction efforts), all of which were located in North America. Interventions had consistent impacts across various indicators of methamphetamine supply and use. Seven of the 15 interventions produced reductions in methamphetamine indicators (ranging from 12% to 77%). Two of the largest impacts were seen following interdiction efforts, involving the closure of rogue pharmaceutical companies. There was no evidence of a shift into other types of drug use, or injecting use, although the impact on the synthetic drug market was not examined. Null effects were related largely to the existence of alternative sources of precursor chemicals or the availability of imported methamphetamine. **Conclusions** Methamphetamine precursor regulations can reduce indicators of methamphetamine supply and use. Further research is needed to determine whether regulations can be effective outside North America, particularly in developing countries, and what impact they have on the broader synthetic drug market. Improved data on precursor diversion are needed to facilitate the evaluation of precursor regulations.

Keywords amphetamine, law enforcement, methamphetamine, precursors, regulations, substance use, supply.

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INTRODUCTION

Methamphetamine is a highly addictive drug that affects somewhere between 14 and 53 million people globally [1]. World-wide production of methamphetamine has been estimated at 290 tons per year, with a retail value of around US$28 billion [2]. Less than 10% of this supply is believed to be interdicted [1]. One of the difficulties controlling methamphetamine supply is the ease with which the drug can be manufactured using readily available chemicals, and the lucrative nature of such ventures [1,3–5].

A major strategy to reduce methamphetamine supply involves regulating the chemicals used in its manufacture [4]. Methamphetamine can be synthesized from a range of chemicals, many of which have legitimate uses, and which can be obtained from various sources (e.g. falsifying import licences, theft from chemical companies, purchasing large quantities of cold-and-flu tablets from pharmacies) [2,4,5]. The most common precursor chemicals are pseudoephedrine and ephedrine, which are used as decongestants in various cold-and-flu medications. Other popular chemical starting points include phenylpropanolamine (PPA) and phenyl-2-propanone (P2P or phenylacetone) [4]. Precursor regulations also cover a range of so-called 'essential chemicals' that are needed in the manufacturing process [5]. The aim of precursor regulations is to prevent the diversion of chemicals from their legitimate uses into clandestine drug manufacture.

Recent research suggests that precursor regulations can be effective, but the evidence is marred by inconsistencies [6–12]. Inconsistencies may arise because regulations are evaluated against different outcomes (e.g. arrests, hospital admissions, price, availability) [13], they vary in their nature (e.g. wholesale versus retail regulations) [11] or there may be contextual factors that impact on their effectiveness (e.g. the availability of imported methamphetamine) [14]. Also, the impact of regulations is impermanent, being undermined by drug manufacturers' propensity to seek out alternative sources of precursor chemicals [14]. Therefore, study designs need to be sensitive to the transient impacts produced by precursor regulations [15].

This systematic review examines the evidence around the effectiveness of methamphetamine precursor regulations in reducing illicit methamphetamine supply and use, and it makes recommendations for future research in this area.

METHOD

Search strategy

Twelve electronic databases were searched with the assistance of a librarian (CINCH-Health, Criminal Justice Abstracts, EconLit, EMBASE, Google Scholar, JSTOR, LegalTrac, MEDLINE, PAIS International, Project Cork, PsychINFO, Scopus). All searches combined three concept areas: methamphetamine or amphetamine, precursor chemicals and regulations. Search strategies were adapted for each database. When available, subject headings were exploded and combined. For example, the MEDLINE search was: 'methamphetamine' (exp), 'amphetamine' (exp), 'amphetamines' (exp); AND 'precursor$', 'precursor chemical$', 'pre precursor$', 'proto precursor$', 'production$', 'ephedrine' (exp), 'pseudoephedrine' (exp), 'phenylpropanolamine' (exp); AND 'government regulation' (exp), 'legislation' (exp), 'drug legislation' (exp), 'law enforcement' (exp), 'drug and narcotic control' (exp). The search was restricted to English language articles published between January 1970 and October 2010. We also hand-searched the latest editions of key journals and the reference lists of papers that were included in the review. The full search strategy and review protocol are available from the authors on request.

Inclusion criteria

To be eligible for inclusion, studies must have examined the impact of a regulation pertaining to chemicals used in the manufacture of methamphetamine or amphetamine. Outcomes needed to relate to methamphetamine use or supply. Article titles/abstracts were screened for relevance by one author (R.S.). The eligibility of full-text papers was subsequently assessed independently by two authors (R.M. and D.B.), including those papers where relevance was unclear. Ties were broken by R.S. Unpublished papers were excluded. Studies also needed to meet minimum quality criteria (see 'Quality assessment').

Quality assessment

The quality of each study was assessed independently by two authors (R.M. and D.B.) using the guidelines of the Cochrane Effective Practice and Organization of Care Group (EPOC) of The Cochrane Collaboration [16]. Where necessary, authors were contacted to clarify the methodology of the study. Differences were resolved though discussion and consensus.

Studies were excluded from the analysis if they did not meet the minimum inclusion criteria for an EPOC review [16]. That is, studies must have been a randomized controlled trial, a controlled clinical trial, a controlled before–after study or an interrupted time–series study. Interrupted time–series studies needed to have a clearly defined point in time when the intervention occurred and at least three data points both before and after the intervention [16].

EPOC guidelines were also used to assess the quality of included studies. For interrupted time–series designs these guidelines covered the appropriateness of the analysis, the number of data points pre- and post-intervention, specification of the intervention shape, assessment of the primary outcome, completeness of the data set, reliability of the outcome measure, protection against detection bias and protection against secular changes.

Data extraction

Study details were extracted using a standardized form [17] covering study design, location, outcome measures, sample size, analysis, results and limitations. Data were extracted separately for each intervention and outcome measure.

Intervention effects

The strength of the evidence for interventions was based on study quality, the number of outcome measures and the consistency of results for different outcome measures, the lack of change in comparison series and the size of the intervention effect. The size of the intervention effect was described in a relative sense as being small (up to 20%), moderate (around 30–40%) or large (50+ %). Post-regulatory changes were as reported by the study authors.

RESULTS

Quality assessment

Twenty relevant studies were identified, of which only 10 met the minimum EPOC inclusion criteria [6–12,18–20] (Fig. 1). The two grey literature studies [21,22] were excluded because these reports did not contain enough methodological detail to enable a quality assessment. Excluded studies [13,21–27] are summarized separately.

The 10 studies that met the EPOC inclusion criteria [6–12,18–20] were all conducted in North America and seven of the 10 were conducted by the same group of researchers (i.e. Cunningham and colleagues) [6–12]. All these seven studies [6–12] met the EPOC quality guidelines for appropriate data analysis; they used long time–series and narrow time intervals that would have been sensitive to transient intervention effects, and they allowed for various shaped intervention effects (e.g. gradual, abrupt, lagged). The three remaining studies [18–20] did not use analyses that would have been sensitive to the type of transient, non-linear intervention effects seen after precursor regulations [18–20], and one of these studies also suffered sampling and measurement limitations [18]. Other specific quality issues are noted below.

- Precursor regulations were embedded within broader drug control legislations which often included subsidiary drug laws that may have contributed to intervention effects.
- Regulations often had several implementation dates (for different aspects of the regulation) or they were implemented over a period of time, and this would have diluted intervention effects.
- None of the studies provided a priori hypotheses about the expected shape of the intervention effect, took into account the nature of the intervention or the timeframe over which it was implemented. The persistence or duration of the intervention effect was not documented systematically.
- No study documented the extent to which regulations were implemented/enforced or reduced precursor diversion.
- There was a lack of studies examining outcomes proximal to methamphetamine production (e.g. clandestine laboratory detections, types of precursors used manufacture).
- Studies relied on indirect indicators of methamphetamine use, which are biased toward heavier users of the drugs and impacted on by health and law enforcement practices [28].

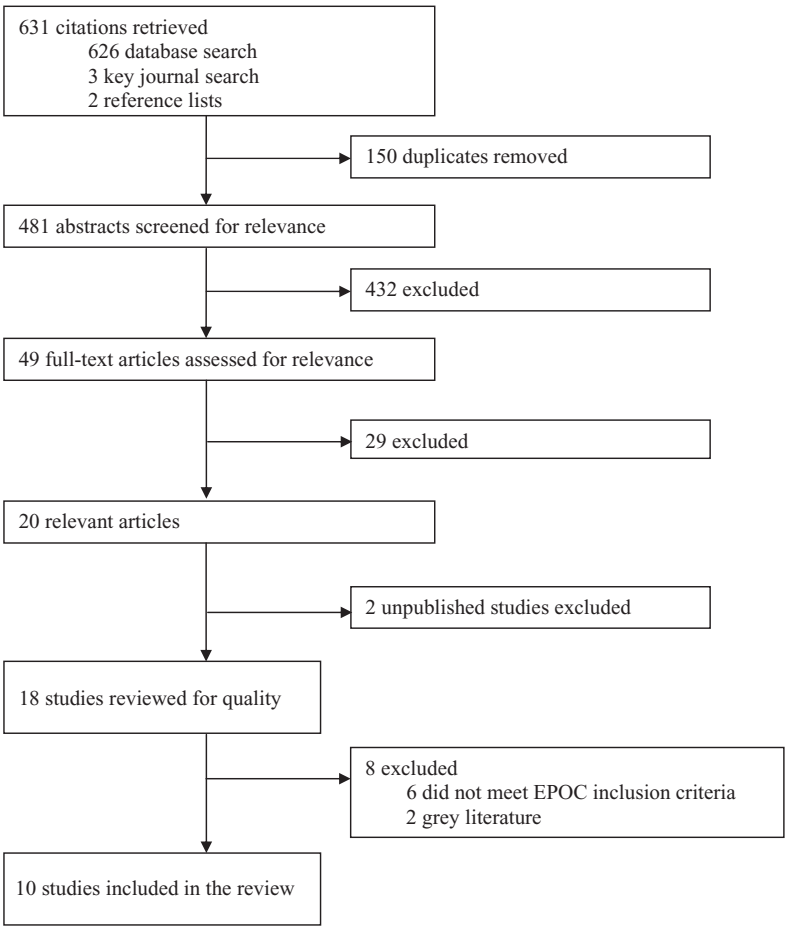

Figure 1 Selection of studies for the review; EPOC: Effective Practice and Organization of Care Group

- Methamphetamine hospital and arrest data were not specific to methamphetamine, including some incidents relating to other drugs. Importantly, hospital data included admissions for the precursor chemicals that were subject to regulation (i.e. pseudoephedrine and ephedrine), the legitimate use of which may have decreased in response to restrictions, inflating intervention effects.
- It was assumed that methamphetamine treatment demand declines in response to reduced methamphetamine supply, although this is consistent with the available evidence [19].

Outcomes by intervention

Most studies examined more than one regulation (or related enforcement effort), and consequently we collated findings from various studies to examine the outcomes for each intervention. Fifteen interventions were evaluated, including 13 precursor regulations and two related enforcement efforts (both involving 'rogue' pharmaceutical companies), the details of which can be found in Table 1. All interventions occurred between 1989 and 2008 and were located in North America. Outcome measures included both indicators of methamphetamine use (treatment admissions, hospital admissions, arrests, toxicology) and supply (price, purity, seizures and detections of clandestine laboratories). One study examined changes in the route of methamphetamine administration.

Each intervention produced reasonably consistent impacts across various indicators of methamphetamine use and supply (Table 2). Seven of the 15 interventions were effective. The reduction in methamphetamine indicators seen following these interventions varied from 12% to 77%. The most substantial impacts were seen following a series of regulations implemented in the United States during the 1990s, one of which coincided with a large-scale precursor seizure and the closure of a rogue pharmaceutical company. A further rogue pharmaceutical company closure in Mexico had a similarly large impact (Table 3). Eight interventions were deemed ineffective, although there were often circumstantial factors or methodological limitations that could account for null effects, as discussed below.

US federal regulations

The strongest evidence in favour of precursor regulations was based on a series of regulations implemented in the United States during the 1990s. These regulations were unique in that they were comprehensive (covering various aspects of importation, wholesale and retail distribution); they were iterative, with regulations updated to close loopholes and to respond to shifts in drug manufacturing methods; they included measures to enforce regulations, and they were embedded within broader drug control frameworks that increased law enforcement capability to intervene in cases of precursor diversion.

1 The Chemical Diversion and Trafficking Act (CDTA) [29] was implemented in 1989 [30] to regulate the import/export and wholesale distribution of precursors. The CDTA was effective in reducing methamphetamine indicators [7,8]. Concurrent increases in the price and decreases in the purity of methamphetamine [11] suggest that these changes were mediated by reduced methamphetamine supply. However, the CDTA was accompanied by a more general downward trend in illicit drug indicators, which is consistent with it being part of a broader initiative to combat illicit drug use [29].

2 The subsequent Domestic Chemical Diversion Control Act (DCDCA) [31] substantially tightened wholesale and import/export regulations, and introduced new retail level restrictions, particularly for products containing ephedrine as the single active ingredient, which had become the primary precursor used in illicit methamphetamine production. The implementation of the DCDCA in 1995 [32] further reduced methamphetamine indicators [7–9], an effect that again appeared to be mediated by a reduction in methamphetamine supply, with concurrent increases in price and decreases in purity [11].

3 Under the rubric of the DCDCA, law enforcement authorities took action against a rogue chemical company in the United States and seized 25 tons of precursors (equivalent to around 13 tons of pure methamphetamine) [19]. This enforcement coincided with the implementation of the DCDCA, as evaluated above [7–9,11], and was associated similarly with a reduction in methamphetamine indicators; the purity of methamphetamine dropped from 90% to 20% and the price per pure gram increased from around US$30 to US$100 [19]. It is therefore it is not possible to know to what extent changes seen after the DCDCA were due to action against the rogue company or the broader regulatory framework of the DCDCA.

4,5 In 1996 the Comprehensive Methamphetamine Control Act (MCA) regulated the retail of pharmaceutical products containing ephedrine and pseudoephedrine that had remained exempt from earlier regulations, and which had emerged as a source of precursor chemicals used in clandestine methamphetamine manufacture [33,34]. The MCA was implemented in two parts. The first part regulated products containing ephedrine in combination with other active ingredients [33]. However, because the use of ephedrine in clandestine drug manufacture

Table 1 Description of the interventions.

No.	*Description of intervention*	*Effective date*	*Chemicals regulated*
US Federal			
1	Implementation of the Chemical Diversion & Trafficking Act (CDTA) [30] This Act required that suppliers (importers, exporters, manufacturers and distributors): ^Keep records of sales involving precursors, essential chemicals, manufacturing equipment, make these records available for inspection, and report losses and suspect transactions. Law enforcement authorities were given the right to inspect records, suspend importation or exportations, and disqualify customers ^^Notify authorities 15 days in advance of import and export of precursors or essential chemicals exceeding a nominated threshold Exemptions applied for medical, commercial, scientific, or other legitimate uses of precursors and essential chemicals	^August 1989 ^^October 1989	Precursor: anthranilic acid, benzyl cyanide, ephedrine, ergonovine, ergotamine, N-acetylanthranilic acid, norpseudoephedrine, phenylacetic acid, phenylpropanolamine, piperidine, pseudoephedrine, 3,4-methylenedioxyphenyl-2-propanone Essential chemicals: acetic anhydride, acetone, benzyl chloride, ethyl ether, hydriodic acid, potassium permanganate, 2-butanone, toluene
2	Implementation of the Domestic Chemical Diversion Control Act (DCDCA) [32] The DCDCA substantially tightened reporting and enforcement procedures for precursors and essential chemicals, introduced retail level restrictions and security provisions around storage (including keeping retail products behind the counter). Regulations were amended to cover products containing ephedrine as the single active ingredient, which were exempt from the previous regulations. Ephedrine (and other precursors) remained except from regulation if they were combined with other therapeutic ingredients (i.e. combined products)	August 1995	Precursors: as above + methylamine, ethylamine, propionic anhydride, insosafrole, safrole, piperonal, N-methylephedrine, N-methylpseudoephedrine, hydriodic acid, benzaldehyde, nitroethane Essential chemicals: as above + hydrochloric acid, sulfuric acid, methyl isobutyl ketone (hydriodic acid removed)
3	Action against rogue pharmaceutical company and large-scale seizure [19]: ^In May 1995 a federal search and seizure warrant was executed for Pennsylvania-based Clifton Pharmaceuticals, a pseudo/ephedrine tablet manufacturer. 25 metric tons of pseudo/ephedrine, as well as large quantities of phenylpropanolamine, were seized. On 31 May, the DEA executed search warrants for a Florida-based mail-order corporation (XLI), seizing more than 500 cases of pseudoephedrine ^^Distribution was shut down in August	^May 1995 ^^August 1995	Precursors: ephedrine, pseudoephedrine, phenylpropanolamine
4,5	Comprehensive Methamphetamine Control Act (MCA) [33] The MCA regulated combination products containing precursors that were exempt under the previous regulations: ^Thresholds were introduced for the wholesale of ephedrine and the retail of combination products containing ephedrine (1 kg and 24 g, respectively) alongside increased reporting regulations for transactions involving pseudo/ephedrine or phenylpropanolamine ^^Regulations expanded to include products containing pseudoephedrine and phenylpropanolamine (except for blister packs or other small packages)	^October 1996 ^^October 1997	Precursors: as per the DCDCA Essential chemicals: as per the DCDCA + acetic anhydride, acetone, benzyl chloride, ethyl ether, potassium permanganate, 2-butanone, toluene, iodine and hydrochloric gas
6	Methamphetamine Anti-Proliferation Act (MAPA) [36] The retail transaction threshold for products containing pseudoephedrine or phenylpropanolamine was reduced from 24 g to 9 g; such products were not to be sold in packages greater than 3 g of pseudoephedrine or 3 g of phenylpropanolamine.	October 2001	Precursors: pseudoephedrine, phenylpropanolamine Essential chemicals: nil

Table 1 *Cont.*

No.	*Description of intervention*	*Effective date*	*Chemicals regulated*
US State			
7	2004 Oklahoma House Bill 2176 [38] The distribution of pseudoephedrine was restricted to licensed pharmacists, with a transaction threshold of 9 g within any 30-day period. Purchasers were required to provide photographic identification and sign for purchases. Exemptions applied to liquid, liquid capsule or gel capsules where pseudoephedrine was not the only active ingredient	April 2004	Precursors: pseudoephedrine
8	2005 Texas House Bill 164 [39]. Only licensed pharmacies permitted to engage in over-the-counter sales; sales limited to two packages or 6 g; products to be stored behind the counter or in a locked case; purchasers required to be 16+ years, provide photographic identification and sign a logbook	August 2005	Precursors: ephedrine, pseudoephedrine, norpseudoephedrine
Canada			
	Precursor Control Regulations (under the Controlled Drugs and Substances Act) [40] Three successive regulations were introduced around the distribution of wholesale precursors and essential chemicals:	^January 2003 ^^July 2003 ^^^January 2004	Precursors: acetic anhydride, N-acetylanthranilic acid, anthranilic acid, ephedra, ephedrine, ergometrine, ergotamine, isosafrole, lysergic acid, 3,4-methylenedioxyphenyl-2-propanone, phenylpropanolamine, 1-phenyl-2-propanone, phenylacetic acid, piperidine, piperonal, potassium permanganate, pseudoephedrine, safrole Essential chemicals: acetone, ethyl ether, hydrochloric acid, methylethylketone, sulphuric acid, toluene
9	^The licensing of precursor manufacturers, packagers and sellers; comprehensive record keeping around the use/movement of precursors. Exemption was provided for the treatment of medical conditions up to specified thresholds: 20 g of ephedra, 0.4 g of ephedrine, 3 g of pseudoephedrine		
10	^^'End-use declarations' had to be completed by unlicensed dealers who were purchasing precursors in quantities in excess of a specified threshold; verification of customer identity required		
11	^^^The sale and provision of essential chemicals was restricted to registered dealers. Permits were required to export to specific destinations (except if preparations contained up to 30% precursor). Record-keeping requirements were extended to essential chemicals		
Mexico			
12	Pseudoephedrine regulations [12]: ^Imports of pseudoephedrine were limited to match legitimate consumption ^^Customers registered in a federal computerised data system; transaction threshold of 60 mg per product per day; theft, loss, diversion or extraordinary sales to be reported immediately; monthly electronic records of sales to be submitted to government; federal officials given immediate access to records upon request	^November 2005 ^^February 2006	Precursors: pseudoephedrine
13	Action against rogue pharmaceutical company [12] Law enforcement action against Zhenli Ye Gon, the head of the 'rogue' pharmaceutical company, Unimed Pharm Chem de México, suspected of unlawfully importing pseudoephedrine. More than US$200 million in cash was seized and the Mexican government filed multiple criminal complaints involving the falsification import permits related to pseudoephedrine	March 2007	Precursors: pseudoephedrine
14	Prescription required to obtain medications containing pseudoephedrine [12]	September 2007	Precursors: pseudoephedrine
15	Prohibition of pseudoephedrine and ephedrine [43]	June 2008	Precursors: ephedrine, pseudoephedrine

Table 2 Outcomes by intervention (excludes cross-border comparisons).

No.	*Intervention*	*Methamphetamine outcome measure*	*Direction of the effect*	*Magnitude*	*Comparison Group*	*Location*	*Study*
US federal regulations							
1	Implementation of the Chemical Diversion & Trafficking Act	Hospital admissions	Decrease	35%[c]	–	California	[7]
		Arrests[a]	Decrease	44%[c]	Decrease for heroin and cocaine but not marijuana	California	[8]
		Purity	Decrease	17% points[c]	Decrease in heroin and cocaine purity	US (continental)	[11]
		Price[b]	Increase	$93[c]	–	US	[11]
2	Implementation of the Domestic Chemical Diversion Control Act	Hospital admissions	Decrease	48–71%[c]	–	California, Nevada, Arizona	[7]
		Treatment admissions (voluntary)	Decrease	39%	No change for cocaine, heroin or alcohol	California	[9]
		Arrests[a]	Decrease	51%[c]	No change for marijuana heroin or cocaine	California	[8]
		Purity	Decrease	68% points[c]	Decrease for cocaine (trend only) but not heroin	US (continental)	[11]
		Price[b]	Increase	$35[c,d]	–	US	[11]
		Route of administration	Number: decrease for all routes Proportion: decrease for smoking and snorting, increase for injecting	–	No change in route of heroin administration	California	[10]
3	Action against rogue pharmaceutical company and large-scale seizure	Hospital admissions	Decrease	50%	No change in marijuana, heroin or cocaine; small increase in alcohol	California	[19]
		Treatment admissions	Decrease	35%	No change in other drug treatment admissions	California	[19]
		Toxicology on arrestees	Decrease	55%	No change in marijuana, heroin or cocaine	Cities in California[e]	[19]
		Arrests[a]	Decrease	50%	No change in cocaine or heroin; increase in marijuana	California	[19]
		Purity	Decrease	70% points	–	California	[19]
		Price	Increase	US$70	–	California	[19]
4	Comprehensive Methamphetamine Control Act–Ephedrine regulation	Hospital admissions	No change	NA	–	California, Nevada, Arizona	[7]
		Arrests[a]	No change	NA	No change in marijuana, heroin or cocaine	California	[8]
		Purity	No change	NA	No change in heroin or cocaine purity	US (continental)	[11]
		Route of administration	Number: increase for smoking; no change for other routes. Proportion: increase for smoking; decrease for snorting	–	No change in route of heroin administration	California	[10]

Table 2 *Cont.*

No.	Intervention	Methamphetamine outcome measure	Direction of the effect	Magnitude	Comparison Group	Location	Study
5	Comprehensive Methamphetamine Control Act—Pseudoephedrine regulation	Hospital admissions	Decrease	25–77%[c]	–	California, Nevada, Arizona	[7]
		Treatment admissions (voluntary)	Decrease	31%	No change in cocaine, heroin or alcohol	California	[9]
		Treatment admissions	No change	NA	–	Texas	[12]
		Arrests[a]	Decrease	60%[c]	No change in cocaine, heroin or marijuana	California	[8]
		Purity	Decrease	29% points[c,d]	No change in heroin or cocaine purity	US (continental)	[11]
		Price[b]	Increase	$76[c,d]	–	US	[11]
		Route of administration	Number: decrease for snorting; no change for other routes. Proportion: decrease for snorting, increase for injecting.	–	Brief decline in number of heroin smokers	California	[10]
6	Methamphetamine Anti-Proliferation Act	Clandestine laboratories	No change	NA	–	US[f]	[20]
		Amount seized	No change	NA	–	US[f]	[20]
		Treatment admissions	No change	NA	–	US[f]	[20]
		Purity	No change	NA	Increase in cocaine and not heroin	US (continental)	[11]
		Purity	Increase	9% points	–	US[f]	[20]
		Price[b]	No change	NA	–	US	[11]
		Price[b]	Decrease	US$86	–	US[f]	[20]
US state regulations							
7	Oklahoma House Bill	Toxicology: number of urine screens positive for amphetamine[g]	Increase	14–19%	–	Hospital in Oklahoma	[18]
8	Texas House Bill	Treatment admissions	No change	NA	–	Texas	[12]
Canadian regulations							
9	Licensing of precursor suppliers	Hospital admissions	No change	NA	No change for opioids, cocaine or alcohol	Canada	[6]
10	End-use declarations	Hospital admissions	Increase	20%	No change for opioids, cocaine or alcohol	Canada	[6]
11	Essential chemical regulations	Hospital admissions	Increase	21%	No change for opioids, cocaine or alcohol	Canada	[6]
Mexican regulations							
12	Pseudoephedrine regulations	Treatment admissions	Decrease	12%	No change in heroin, cocaine or alcohol	Mexico, Texas	[12]
13	Action against rogue pharmaceutical company	Treatment admissions	Decrease	56%	No change in heroin, cocaine or alcohol	Mexico, Texas	[12]
14	Prescription requirement for pseudoephedrine	Treatment admissions	No change	NA	Not reported	Mexico, Texas	[12]
15	Prohibition of pseudoephedrine and ephedrine	Treatment admissions	Decrease	15%	Decrease in heroin, cocaine and alcohol	Mexico, Texas	[12]

The magnitude of intervention effects are pre- versus post-percentage change except for purity and price which are expressed as absolute change. [a]Included offences for drugs other than methamphetamine. [b]Price per pure gram. [c]Estimates based on ARIMA model predictions. [d]Trend only ($P < 0.10$). [e]San Jose, San Deigo and Los Angeles. [f]Excluding California. [g]Included ecstasy and certain antibiotics. NA: not available.

Table 3 Summary of intervention effects.

No.	*Intervention*	*Year*	*Type of intervention*	*Effective*	*Effect size*	*Strength of the evidence*	*Studies*
US federal							
1	Chemical Diversion & Trafficking Act	1989	Import/export, wholesale	Yes	Moderate	Moderate	[7,8,11]
2	Domestic Chemical Diversion Control Act	1995	Import/export, wholesale, retail	Yes	Large	Strong	[7–11]
3	Action against rogue pharmaceutical company and large-scale seizure	1995	Enforcement	Yes	Large	Moderate	[19]
4	Comprehensive Methamphetamine Control Act—Ephedrine regulation	1996	Retail	No		Strong	[7,8,10,11]
5	Comprehensive Methamphetamine Control Act—Pseudoephedrine regulation	1997	Retail	Yes	Large	Strong	[7–12]
6	Methamphetamine Anti-Proliferation Act	2001	Retail	No		Moderate	[11,20]
US state							
7	Oklahoma House Bill	2004	Retail	No		Weak	[18]
8	Texas House Bill	2005	Retail	No		Moderate	[12]
Canada							
9	Licensing of precursor suppliers	2003	Import/export, wholesale	No		Moderate	[6]
10	End-user declarations	2003	Import/export, wholesale	No		Moderate	[6]
11	Essential chemical regulations	2004	Import/export, wholesale	No		Moderate	[6]
Mexico							
12	Pseudoephedrine regulations	2005/06	Import, retail	Yes	Small	Moderate	[12]
13	Action against rogue pharmaceutical company	2007	Enforcement	Yes	Large	Moderate	[12]
14	Prescription requirement for pseudoephedrine	2007	Retail	No		Moderate	[12]
15	Prohibition of pseudoephedrine and ephedrine	2008	Prohibition	Yes	Small	Weak	[12]

had been largely superseded by pseudoephedrine [34], this regulation did have any impact [7,8,11]. The second part of the MCA, which went into effect in 1997, regulated the use of the pseudoephedrine products, which had become the choice precursor for clandestine chemists [34]. This component of the MCA was effective, being followed by a decrease in methamphetamine indicators [7–9,12], a reduction in purity and an abrupt increase in price [11]. In contrast, the MCA did not affect methamphetamine indicators (treatment admissions) in Texas; however, this null effect could be attributed to the low number of treatment admissions at the time [12] and/or the supply of methamphetamine from neighbouring Mexico [12,35].

6 Tighter retail restrictions over pseudoephedrine were implemented through the Methamphetamine Anti-Proliferation Act (MAPA) [36]. MAPA was enacted in 2000, which brought into effect a range of drug control measures around methamphetamine. MAPA regulations to restrict the retail of pseudoephedrine (from 24 g to 9 g) came into effect in 2001. While these regulations were effectively in place from 2001, the US Drug Enforcement Agency did not issue rules around their implementation until 2003 [37]. Two studies evaluated MAPA, one using the enactment date of 2000 [20] and the second using the 2001 effective date for the pseudoephedrine retail regulation [11]; neither found an impact. This null effect may have been due to misspecification of the intervention date, particularly if there were problems with the enforcement of the retail restrictions prior to the final rules implemented by the US Drug Enforcement Agency in 2003. The MAPA regulations were also lax. In comparable situations elsewhere, lax retail regulations have been sidestepped by drug trafficking syndicates who organize gophers to purchase unregulated quantities of pharmaceuticals from multiple pharmacies [21]. A final consideration is that MAPA came into effect the month after the 9/11 attacks in the United States, and this may have affected capacity to implement/enforce the regulations.

US state regulations

7,8 Two US state regulations were examined. The first found an increase in the number of positive urine

screens for amphetamines among emergency room patients in Oklahoma after the regulation of retail products containing pseudoephedrine [18,38]. This study suffered sampling and measurement limitations and did not use an appropriate method of data analysis. The second regulation addressed the retail of precursors in neighbouring Texas [39], and this was found to have no impact on methamphetamine treatment admissions. The impact of both regulations was likely to have been diluted by the availability of imported methamphetamine from Mexico [12,35].

Canadian regulation of precursor chemicals

9–11 In 2003/04 Canada implemented a series of regulations around the wholesale of precursors and essential chemicals [40]. These regulations had no significant impact on methamphetamine indicators [6]. There are a number of possible explanations for this null effect. First, domestic methamphetamine production in Canada was relatively limited at the time [41]. Secondly, precursor chemicals were being imported from Asia (in addition to being sourced domestically) [41] and this illegal importation may have remained unhindered by domestic regulations. Finally, the regulations may have been too lax, requiring record-keeping and licensing of suppliers, but without scope for associated enforcement activities (which was a feature of the effective wholesale regulations in the United States) [40]. The Canadian regulations were also associated with small shifts in methamphetamine purity in the United States, but these effects had large confidence limits and were inconsistent in their direction.

Mexico regulations

12–15 Several regulations over pseudoephedrine have been examined against methamphetamine treatment admissions in Mexico and in neighbouring Texas, which receives most of its methamphetamine supply from Mexico [12]. These laws supplemented earlier, broader regulations that covered a range of precursors and essential chemicals [42]. The 2005/06 regulations over pseudoephedrine were associated with a small decline in methamphetamine treatment admissions in both Mexico and in Texas (12% and 11%, respectively) [12]. Subsequent enforcement actions relating to a rogue precursor chemical company in 2007, and enforcement around falsified importation permits, was associated with a larger decrease (56% and 48% in Mexico and Texas, respectively) [12]. The subsequent prescription requirement for pseudoephedrine was not related to any further reductions in methamphetamine treatment admissions in either location. In 2008 Mexico prohibited pseudoephedrine entirely [43], resulting in only a small decline in treatment admissions in Mexico, which was accompanied by declines in comparison drug series, casting doubt that this reduction was attributable to the precursor regulation. This regulation had no impact on methamphetamine treatment admissions in Texas, although the authors explain that this cross-border impact might be delayed and their time–series did not include sufficient data to detect a lagged intervention effect [12]. The smaller impacts of the Mexican precursor regulations (cf. US regulations) could be because their implementation was undermined by local corruption [43], or because of the tenacity of local drug cartels and their capacity to source methamphetamine/ precursor chemicals from elsewhere in the Americas [1].

Shifts to other drug use or injecting

Based on the current studies, there was no evidence of substitution into the use of other drugs or a shift to injecting drug use after precursor regulations (i.e. to compensate for lower purity). Specifically, indicators of other drug use did not increase when methamphetamine indicators dropped in response to precursor regulations [8–12,19]. Only one study examined the impact on route of administration [10], which found no increase in the number of injecting methamphetamine users attending drug treatment after precursor regulations (Table 2). However, there was a shift to proportionally more injectors than non-injectors in treatment, suggesting that injectors may be less sensitive to reductions in methamphetamine supply.

Excluded studies

The outcomes from excluded studies [13,23–27], most of which were also conducted in the United States, were generally consistent with the more rigorous studies included in our analysis. Reuter & Caulkins [13] reported on a range of indicator data pre- and post- three precursor regulations (interventions 1, 2 and 5 in Table 1) and found impacts consistent with the more sophisticated studies included in this review [7–11]. Several studies examined changes following state-level retail regulations in the United States, the majority of which were associated with reductions in methamphetamine indicators, including clandestine laboratory detections and workplace amphetamine-positive urine tests [22,24,27]. One

study failed to find reductions in methamphetamine use among a cohort of stimulant users recruited from Arkansas, Kentucky and Ohio after the implementation of regulations in these states [25]. Two studies documented a reduction in clandestine laboratory detections after the a state-level retail regulation in Queensland, Australia [21,23]. A qualitative study in Odessa noted that injecting drug users obtained alternative chemicals from pharmacists to make stimulant drugs in the face of Ukrainian precursor regulations [26].

DISCUSSION

There was strong evidence that certain precursor regulations were effective, but not others. Outcomes were consistent across indicators, with reductions varying from 12% to 77%. There was no evidence of a consequent substitution into other drugs, or a shift to injecting methamphetamine use, although interventions did seem to have comparatively less impact on injectors, possibly reflecting that this group have better access to drug supply or that they are less responsive to reductions in drug availability. A caveat around these findings is that the evidence was derived entirely from North America. This limits the generality of the findings to other regions, particularly developing regions, where drug market factors and constraints over implementing regulations may be vastly different.

None of the studies documented the implementation of regulations or whether they were effective in reducing diversion, instead relying on downstream indicators of methamphetamine supply and use to infer their efficacy. Consequently there was no way to distinguish between regulations that were ineffective because they were too lax or poorly implemented, and those regulations that failed because of methamphetamine importation from neighbouring geographic regions. This reliance on distal outcomes is undoubtedly driven by the scarcity of good data on precursor diversion. Retail sales are typically subject to commercial in-confidence privacy restrictions, survey data on legitimate consumption are lacking, and data on illegal importation are confounded by seizures unrelated to drug manufacture (e.g. personal use of medications and dietary products) [44]. Improved data in these areas would help inform the development of effective precursor regulations and it would greatly facilitate their evaluation.

The importation of methamphetamine and precursors from neighbouring countries appeared to be a prime factor undermining the effectiveness of precursor regulations. As precursor chemicals become more tightly regulated in many developed nations, criminal syndicates are increasingly taking advantage of weak precursor regulations and limited policing capacity in developing countries to undertake large-scale clandestine methamphetamine production [1,14]. The international trafficking of precursor chemicals from these countries has also become a lucrative criminal enterprise in its own right [14]. A critical consideration is whether precursor regulations can been applied in developing regions, where the capacity for their implementation, and the enforcement of such regulations, may be limited.

The question for future research is not so much whether precursor regulations work, but which regulations work best and in what context. Interventions typically included a raft of regulations targeting different aspects of precursor diversion, and they often coincided with broader drug control laws, these being tailored to local trends in drug manufacture. It was not possible to determine which aspect of a regulation was driving the intervention effect (e.g. whether it was the licensing of wholesale distributors, increased penalties for illegal trafficking, or limiting the retail of pharmaceutical drugs) or whether it was the comprehensiveness of some regulations that rendered them effective. Importantly, one of the most effective regulations [32] coincided with a large seizure of precursor chemicals (25 tons), causing a major disruption to precursor supply in the United States [19]. The closure of a rogue precursor chemical company in Mexico had a similarly large impact [12]. It is therefore not clear to what extent the impact of precursor regulations is mediated by interdiction efforts as opposed to bureaucratic regulatory measures.

Methodological considerations for future research

Only half the precursor regulation evaluations that we identified used appropriate methods. Inadequate study design in time–series analysis can not only miss intervention effects, but it can lead to changes being detected that are due to secular events. These problems are documented elsewhere in detail [15,45], and quality guidelines are provided by the EPOC group [16]. Improved study design is needed in this area of research to ensure that specious results do not confound the evaluation of precursor regulations.

The details of precursor regulations and the context in which they were implemented needs to be documented more carefully. This includes all elements of a regulation (and subsidiary laws) and the time-frames over which they were implemented. Information should be provided, where available, on factors that may have prevented regulations from being fully implemented or enforced. These factors need to be considered when modelling the expected shape of the intervention effect (e.g. immediate versus gradual or delayed). Contextual information on trends in methamphetamine supply, including

manufacturing methods and importation, should be documented to facilitate the interpretation of null effects.

Limitations

Precursor regulations are developed specifically in response to trends in synthetic drug manufacture, and it is therefore difficult to make generalizations about their effectiveness. Regulations that might work in one time and location may fail if implemented in a different context, simply because the nature of methamphetamine manufacture, and the chemicals used in its production, change over time and vary by geographic location [1]. The evidence in this review was derived from North America. The nature and impact of precursor regulations may differ in other regions, such as Europe or Asia, this being affected by the relative availability of other precursors and other drugs, drug trafficking routes in nearby geographic regions, and the *modus operandi* of local criminal syndicates. Clandestine drug manufacture is also becoming more sophisticated, with chemists synthesizing their own precursors from other chemicals (dubbed 'pre-precursors') and there has been an expansion in the type of synthetic drugs manufactured [1].

One factor that has not been examined to date is the relationship between methamphetamine precursor regulations and the expansion of the market for other synthetic stimulant drugs. Existing research considers the impact of regulations on several drug types (cocaine, heroin, cannabis) [8–12,19], but not on ecstasy or other new synthetic stimulants, such as mephedrone, which have become popular alternatives to methamphetamine [46]. In Japan 32 such new synthetic stimulant drugs have been identified and banned since 2007 [47]. The extent to which precursor regulations are driving this shift in the drug market, and whether regulations can successfully respond to such shifts, needs to be explored.

CONCLUSION

Methamphetamine precursor regulations can reduce indicators of methamphetamine supply and use, but their impact is contingent upon the context in which they are implemented, with their effectiveness being undermined by alternative sources of precursor chemicals and imported methamphetamine. The current findings are specific to North America and it remains to be seen whether regulations can be effective outside of this region, particularly in developing countries, where precursor trafficking and methamphetamine manufacture has become a growing concern [1]. Clearer data are needed to monitor the diversion of precursor chemicals *per se*. This would aid the development of precursor regulations and greatly facilitate their evaluation.

Declarations of interest

None.

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